19 September 2024
EMA/464830/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Esperoct

International non-proprietary name: Turoctocog alfa pegol

Procedure No. EMEA/H/C/004883/II/0023

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ABR	annualised bleeding rate
aPTT	activated partial thromboplastin time
AsBR	annualised spontaneous bleeding rate
AUC	area under the curve
BMI	body mass index
BU	Bethesda unit
C30min	FVIII activity 30 min post-dosing
CHO	Chinese hamster ovary
CI	confidence interval
CYP450	cytochrome P450
CV	coefficient of variation
ED	exposure day
EMA	European Medicines Agency
FVIII	coagulation factor VIII
HCP	host cell protein
ICH	International Council for Harmonisation
ISTH	International Society on Thrombosis and Haemostasis
kDa	kilodalton
M	module e.g., Trial 3859 (M 5.3.5.2)
N8	turoctocog alfa; a recombinant factor VIII developed by Novo Nordisk
N8-GP	turoctocog alfa pegol; 40 kDa glycoPEGylated rFVIII
NHP	normal human plasma
PD	pharmacodynamics
pdFVIII	plasma-derived coagulation factor VIII
PEG	polyethylene glycol
PK	pharmacokinetics
PSS	product specific standard
PYE	patient years of exposure
Q3	dosed every third day
Q4D	dosing every fourth day
Q7D	dosing every seventh day
rFVIII	recombinant coagulation factor VIII

rFVIIa	recombinant activated coagulation factor VII
SD	standard deviation
Trial	individual trials in the N8-GP development programme are referenced as trial xxxx (e.g., trial 3859 corresponds to trial ID NN7088-3859).
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novo Nordisk A/S submitted to the European Medicines Agency on 13 March 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include children below 12 years of age for treatment and prophylaxis of bleeding with haemophilia A for Esperoct, including previously untreated patients (PUPs) based on the final results from studies 3776, 4410, 3908, 3859, 3885, 3860, 4033 and 4595. As a consequence, section 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.1 of the RMP has also been submitted. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0142/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0142/2017 was completed.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Daniela Philadelphy Co-Rapporteur: Ewa Balkowiec Iskra

Timetable	Actual dates
Submission date	13 March 2024
Start of procedure:	30 March 2024
CHMP Rapporteur Assessment Report	27 May 2024
PRAC Rapporteur Assessment Report	29 May 2024
PRAC members comments	5 June 2024
CHMP Co-Rapporteur Assessment	6 June 2024
PRAC Outcome	13 June 2024
CHMP members comments	17 June 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 June 2024
Request for supplementary information (RSI)	27 June 2024
MAH's responses submitted on	19 July 2024
CHMP Rapporteur Assessment Report on the MAH's responses	20 August 2024
PRAC Rapporteur Assessment Report on the MAH's responses	20 August 2024
PRAC members comments	28 August 2024
PRAC Outcome	5 September 2024
CHMP members comments	9 September 2024
Updated CHMP Rapporteur Assessment Report	NA
CHMP Opinion	19 September 2024
The CHMP adopted a report on similarity of Esperoct with Roctavian on date (Appendix)	19 September 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Haemophilia A is a rare and serious, X-linked, recessive bleeding disorder that predominantly affects males and is characterised by a deficiency of FVIII. In patients with haemophilia A, the primary platelet-driven haemostasis is not affected, but generation of a stable, fibrin-rich clot is defective because inadequate amounts of thrombin are generated. Affected patients suffer from both spontaneous, non-traumatic bleeding episodes as well as substantially prolonged bleeding episodes upon injury. Rarely, life-threatening bleeding may also occur. Patients exhibit variable clinical phenotypes depending on the extent of residual activity (%) of the deficient FVIII that is used to classify the disease severity (WFH, 2012):

- <1% FVIII activity: severe haemophilia A
- 1% to 5% FVIII activity: moderate haemophilia A
- 5% to 40% FVIII activity: mild haemophilia A

Patients with severe haemophilia A bleed spontaneously into joints and muscles, which often results in permanent, disabling joint damage.

State the claimed therapeutic indication

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

Esperoct can be used for all age groups.

Epidemiology

The overall reported number of haemophilia A patients estimated in the 2013 survey by the World Federation of Haemophilia (WFH) included 107 countries with a total population of 6,461,067,861 and identified 140,313 people with haemophilia A (2.2 per 100,000 individuals). There are currently approximately 30,000 patients in the EU with a mean prevalence of approximately 0.6 patients per 10,000.

Haemophilia A is inherited as an X-linked recessive trait and the main risk factors are therefore family history and a carrier mother. Approximately 30% of patients have no family history of the disease; their disease is presumably caused by new mutations.

Biologic features

The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions. When infused into a haemophiliac patient, factor VIII binds to von Willebrand factor in the patient's circulation. Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed.

Clinical presentation, diagnosis

Haemophilia A manifests as profuse bleeding into the joints and muscles or internal organs, either spontaneously or as the result of accidental or surgical trauma. Recurrent joint bleeding can lead to chronic arthropathy, pain, and loss of function (Bolton-Maggs and Pasi, 2003). The majority of bleeding occurs internally into joints, most commonly hinged joints such as the ankles, knees, and elbows. Serious bleeds also occur in muscles, especially in deep compartments such as the iliopsoas, calf and forearm, and in the mucous membranes in the mouth, gums, nose, and genitourinary tract. Less frequently, life threatening bleeds can occur in or around vital areas or organs such as the gastrointestinal system or enclosed areas like the intracranial or intracerebral spaces. The approximate frequencies of bleeds at the different sites are: 70 to 80% in joints (haemarthrosis), 10 to 20% in muscle, 5 to 10% in the central nervous system, and < 5% for bleeds at all other sites (Srivastava *et al.,* 2013).

Management

Standard treatment for haemophilia A patients is the replacement of the missing protein by infusion of exogenous FVIII concentrates (as plasma-derived FVIII [pdFVIII] or recombinant FVIII [rFVIII] concentrates). Treatment regimens are either on-demand therapy (given when a bleed occurs) or prophylaxis (which consists of regular infusion of FVIII given every 2 to 3 days to prevent bleeding). In the short term, prophylaxis can prevent spontaneous bleeding and in the long term, prophylaxis can prevent bleeding into joints that will eventually lead to debilitating arthropathy.

Prior to the introduction of clotting factor concentrates in the 1960s, the prognosis for haemophilia A patients was poor, average life expectancy being 15 to 25 years. Major advances in the safety of clotting factor products, including the availability of rFVIII concentrates, the availability of comprehensive haemophilia A treatment centres, the institution of routine prophylaxis, the introduction of home treatment, as well as the active roles that patients take in self-advocacy, have enabled patients with haemophilia A to lead a "close to normal" life.

The recent development of FVIII products with extended half-lives has made it possible to maintain higher FVIII activity levels with fewer injections. Two other extended half-life FVIII products are currently licensed (Elocta and Adynovi). Hemlibra (emicizumab) has been recently authorised for routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors and without factor VIII inhibitors.

In addition, an AAV-based gene therapy, Roctavian given as a single administration is approved for the treatment of severe haemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5).

2.1.2. About the product

Turoctocog alfa pegol is a recombinant human factor VIII product, produced in Chinese Hamster Ovary cells (CHO), with a glycoPEGylation on the O-linked glycan in the truncated B-domain. The turoctocog alfa pegol molecule is a polypeptide containing a Heavy chain and a Light chain held together by non-covalent interactions. In native Factor VIII these chains are connected by a native B-domain, while turoctocog alfa pegol has a truncated rFVIII containing 21 amino acids of the native B-domain. When turoctocog alfa pegol is activated by thrombin, the B-domain containing the 40K PEG and the a3-region are cleaved off, thus generating activated factor VIII (rFVIIIa) which is similar in structure to native FVIIIa.

Turoctocog alfa pegol also referred as N8-GP is based on the currently licenced NovoEight (turoctocog alfa) with an extended half-life due to the covalent conjugation of a PEG moiety.

The mechanism of action is based on replacement of the deficient or absent FVIII in patients with haemophilia A.

2.1.3. Development programme compliance with CHMP guidance/scientific advice

The clinical development programme was consistent with available scientific guidelines and received scientific advice.

2.1.4. General comments on compliance with GCP

The MAH has indicated that all trials are carried out in compliance with GCP requirements.

2.2. Non-clinical aspects

No new clinical data were submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1: Tabular overview of clinical studies

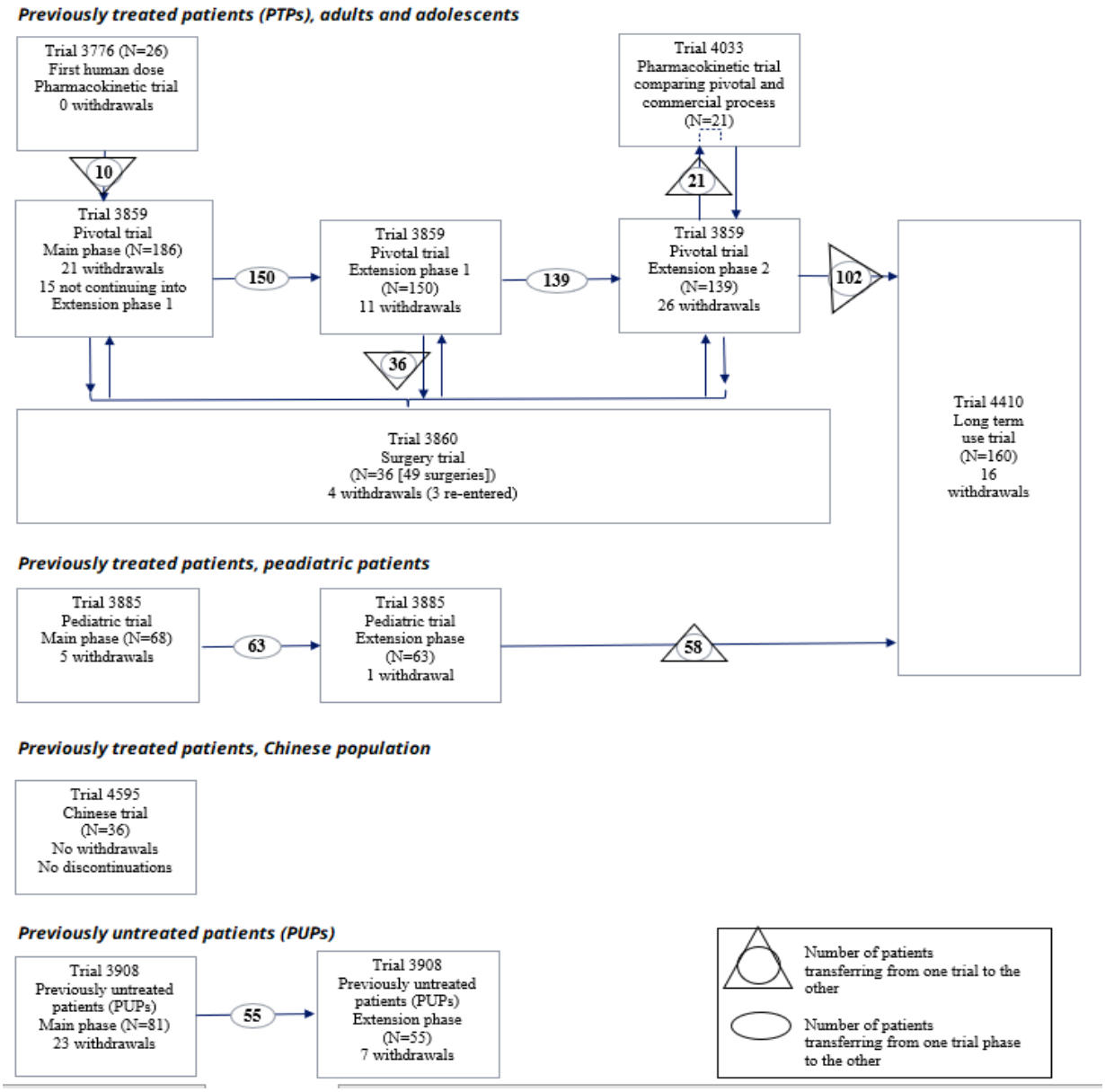
Trial ID/Phase Status	Trial design	N8-GP dose and treatment regimen[a]	Number of patients[b] (age range)
Previously treated patients			
Trial 3885[e]/Phase 3 Main+Ext Full report Completed	<u>Paediatric safety efficacy and PK trial</u> A multinational, open-label, non-controlled trial on safety, efficacy and PK of N8-GP when administered for prophylaxis and treatment of bleeding episodes in previously treated paediatric patients with severe haemophilia A.	Prophylaxis: ~60 IU/kg (50–75 IU/kg) twiceweekly with adjustment to every third day, if necessary Treatment of bleeds: 20–75 IU/kg Single-dose PK: 50 IU/kg	68 patients (0–11 years) PK: 27 patients
Trial 4410[e]/Phase 3b Completed	<u>Long-term safety and efficacy of N8-GP</u> Multi-national, open-label, non-randomised trial investigating the safety and efficacy of N8-GP during continuous use for prevention and treatment of bleeding episodes of previously N8-GP treated severe haemophilia A patients.	Prophylaxis: For <12 years: 60 IU/kg twice-weekly or 50 IU/kg three times weekly For ≥12 years: 50 IU/kg twice-weekly, 50 IU/kg three times weekly Treatment of bleeds: 20–75 IU/kg	160 patients from trials 3859 (N=102) and 3885 (N=58)[d] (A total of 29 patients were children and aged <12 years [from trial 3885] and the remaining 131 were aged ≥12 years (from trials 3859 and 3885] at the time of entry in this trial.
Trial 3776/Phase 1 Completed	<u>First human dose safety and PK trial</u> A multi-centre, open-label, dose escalation trial evaluating safety and PK of three single doses of N8-GP in patients with severe haemophilia A.	Single-dose PK: 25, 50, 75 IU/kg of previous FVIII product and N8-GP	26 patients (20–60 years)
Trial 3859/Phase 3	<u>Pivotal safety efficacy and PK trial in adolescents and adults</u> A multi-centre, open-label, non-controlled trial evaluating	Prophylaxis: 50 IU/kg Q4D or 75 IU/kg Q7D	186 patients

Trial ID/Phase Status	Trial design	N8-GP dose and treatment regimen[a]	Number of patients[b] (age range)
Main+Ext 1+Ext 2 (Full report) Completed	safety and efficacy, including PK, of N8-GP when administered for long-term prophylaxis and treatment of bleeding episodes in patients with severe haemophilia A.	Treatment of bleeds: 20–75 IU/kg Single-dose PK: 50 IU/kg	(12–66 years) PK: 24 patients
Trial 3860/Phase 3 Full report Completed	Surgery trial in adolescents and adults A multi-centre, open-label, non-controlled trial evaluating efficacy and safety during major surgical procedures in patients with severe haemophilia A.	Pre-surgery period: Preoperative dose aiming for a FVIII activity level of 80-100% Post-operative period Days 1–6: At the investigator's discretion, aiming for a FVIII activity level above 50% Days 7–14: At the investigator's discretion	36 patients; (15–69 years)
Trial 4033//Phase 1 Completed	PK and safety of N8-GP from the pivotal and the commercial process A multi-centre, comparative, double-blinded, randomised cross-over trial investigating single-dose PK and safety of N8-GP from the pivotal process and N8-GP from the commercial process in patients with severe haemophilia A.	Single-dose PK: 50 IU/kg Prophylaxis regimen from trial 3859 was allowed between visitsc	21 patients (25–71 years)
Trial 4595/Phase 3b Completed	Trial in Chinese cohort A multi-centre, open-label trial evaluating efficacy, safety and PK of N8-GP when used for treatment and prophylaxis of bleeding episodes in previously treated Chinese patients with severe haemophilia A	Prophylaxis: 50 IU/kg (once every 4 days; changed to twice-weekly at investigator's discretion) Treatment of bleeding episodes: 20-75 IU/kg. Single-dose PK: 50 IU/kg (visit 2a) Steady-state PK: 50 IU/kg (visit 7)	36 patients (≥12years) PK: 15 patients
Total number of unique previously treated patients			**270**
Previously untreated patients			
Trial 3908[e]/Phase 3a Main + Ext (Full report) Completed	Trial assessing safety and efficacy in previously untreated patients An open-label, single-arm multi-centre non controlled trial investigating safety and efficacy of N8-GP in previously untreated paediatric patients with severe haemophilia A.	Main phase: Pre-prophylaxis (on-demand or slow start prophylaxis): 60 IU/kg (50-75 IU/kg), >1 week between doses Prophylaxis: 60 IU/kg (50–75 IU/kg) every third day, twice-weekly, every fourth day, every fifth day, every sixth day or every seventh day Treatment of bleeds: 20–75 IU/kg	81 patients (<6 years)

[a]Bleeds were treated according to the severity and location of the bleed. All doses of N8-GP were administered by intravenous route of administration. Additional doses for treatment of a bleed could be given at the investigator's discretion.
[b]All patients had severe haemophilia A with FVIII activity <1%.
[c]Trial 4033: Patients were recruited from trial 3859 and returned to trial 3859 after completion of the trial; prophylactic treatment from trial 3859 was allowed between visits in trial 4033.
[d]Trial 4410: Patients were recruited from trials 3859 and 3885.
[e]Trials that include children <12 years of age.
Abbreviations: Ext = extension; PK = pharmacokinetics; (Q7D = every seventh day dosing;
Q4D = patients starting dose was every fourth day, subsequently patients could switch to twice-weekly.

The flow of patients in the development programme is presented below. All Previously Treated Patients (PTPs) entered the clinical development programme through trials 3776, 3859 and 3885. Patients from the first human dose trial 3776 participated in the phase 3 trial 3859. Patients from trial 3859 requiring major surgery participated in the surgery trial 3860 and, after the surgery had been completed, returned to trial 3859. A subset of patients from trial 3859 also participated in the PK trial 4033, and after completion of this trial returned to trial 3859. Trial 3885 was conducted exclusively in children aged <12 years and after completion of this trial 58 patients were transferred to the trial 4410 (in addition to the 102 patients who had completed trial 3859). As many patients participated in more than one trial, the sum of patients in the individual trials is higher than the total number of unique patients.

Figure 1: Flow of patients in the N8-GP clinical development programme



Notes: Prior to entering the extension phase(s) of the trials, patients had to re-consent to continue. Those who did not re-consent are denoted as 'not continuing' in the figure.
All the patients enrolled in trials 3860 and 4033 were recruited from trial 3859 and re-entered trial 3859 upon completion of trial 3860 or trial 4033. Three (3) patients withdrew from trial 3860 as they had their surgery postponed/cancelled of whom 2 patients re-entered trial 3860 to have surgery done at a later stage. Nine (9) patients entered trial 3860 more than once from different phases of trial 3859.
Patients enrolled to trial 4410 after completion of trials 3859 and 3885.
Abbreviation: N: Number of exposed patients.

2.3.2. Pharmacokinetics

TRIAL ID: NN7088-3885

Trial 3885 was a multinational, open-label, non-controlled trial on safety, efficacy and pharmacokinetics of NNC 0129-0000-1003 (turoctocog alfa pegol) in previously treated paediatric patients with severe haemophilia A.

Since weight-adjusted clearance of coagulation factors is higher in children than in adolescents and adults, the dose of N8-GP selected for prophylactic treatment in the paediatric trial 3885 was 60 IU/kg (50–75 IU/kg) administered twice weekly (enabling for whole mL dosing).

FVIII activity

A total of 27 patients (40%) were enrolled for two PK assessments (PK profiles), i.e., one with their previous FVIII product, and one with N8-GP, during the main phase of the trial. The patients' previous FVIII product was defined as the product used for prophylaxis and/or treatment of bleeds prior to enrolment into the trial and could be either a recombinant or a plasma-derived FVIII product.

In the main phase CTR, PK data were reported in-text only for the chromogenic assay using normal human plasma (NHP) as calibrator. During the clinical development program, it was demonstrated that the specific chromogenic assay set-up employed with NHP as calibrator overestimated FVIII activity. After the main phase of the trial, the method of analyses of the half-life estimates were changed to the population-based method since this is regarded to be the most suitable method in the present trial population.

Table 2: PK parameters for N8-GP (chrom PSS) and previous FVIII product (chrom NHP) by age group – full analysis set

	Younger children (0 - 5 years)	Older children (6 - 11 years)	Total
Number of patients	15	12	27
AUC(0-inf) (IU*h/mL)			
Previous FVIII product, N	14	11	25
Estimate	11.628	12.203	11.877
95% CI	9.170 ;14.744	9.336 ;15.951	9.969 ;14.151
N8-GP, N	13	11	24
Estimate	21.489	25.026	23.042
95% CI	16.785 ;27.511	19.145 ;32.713	19.265 ;27.559
CL (mL/h/kg)			
Previous FVIII product, N	14	11	25
Estimate	4.322	3.867	4.115
95% CI	3.404 ; 5.486	2.955 ; 5.061	3.452 ; 4.906
N8-GP, N	13	11	24
Estimate	2.601	2.386	2.501
95% CI	2.030 ; 3.333	1.823 ; 3.123	2.091 ; 2.993
Inc. Rec. at 60 min ((IU/mL)/(U/kg))			
Previous FVIII product, N	13	12	25
Estimate	0.017	0.022	0.019
95% CI	0.014 ; 0.021	0.018 ; 0.027	0.017 ; 0.022
N8-GP, N	13	12	25
Estimate	0.018	0.020	0.019
Half-life estimates using the population based method			
Previous FVIII product*			
N	14	12	26
Mean (SD)	7.3 (1.37)	7.6 (1.45)	7.5 (1.38)
Median	7.0	7.2	7.0
Min ; Max	4.5 ; 9.5	5.8 ; 9.9	4.5 ; 9.9
CV%	20.1	19.1	19.2
Geometric Mean	7.2	7.5	7.3
Estimate**	7.3	7.6	7.4
N8-GP*			
N	13	12	25
Mean (SD)	13.9 (2.83)	14.6 (3.96)	14.2 (3.36)
Median	13.0	13.3	13.1
Min ; Max	10.6 ; 18.3	10.9 ; 24.0	10.6 ; 24.0
CV%	20.4	25.0	22.3
Geometric Mean	13.6	14.1	13.9
Estimate**	13.6	14.2	13.9
N8-GP/Prev. FVIII product			
Ratio	1.856	1.876	1.866

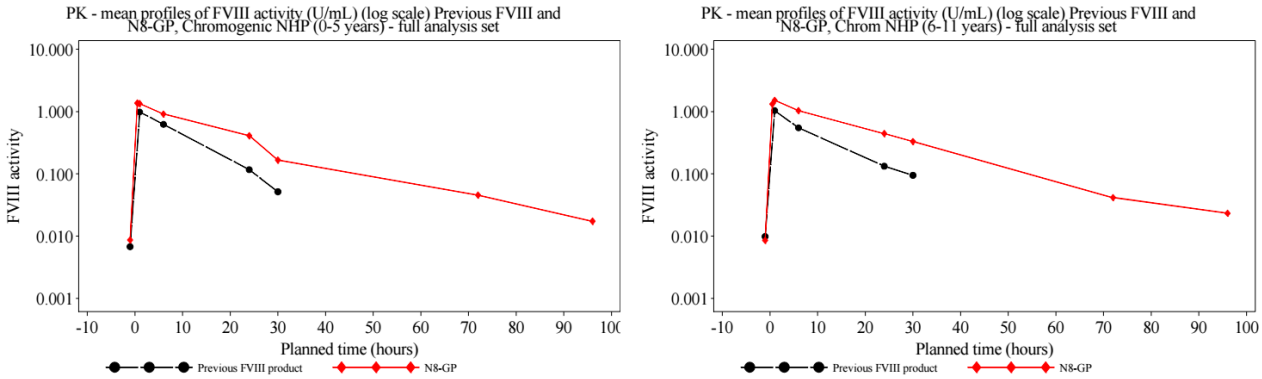
For previous FVIII product chromogenic assay with normal human plasma calibrator was used while for N8-GP chromogenic assay with product specific calibrator was used. * A non-linear mixed effect model was applied to estimate the terminal half-life, where the FVIII activity level was assumed to follow a mono-exponential decay, and between patient variation was allowed for the volume of distribution and elimination rate. Age-group was treated as fixed effect when the terminal half-life was estimated for each age-group. Observations below LLoQ were treated as left-censored data. The summary statistics are based on individual predicted values obtained from the model.** The t½ for previous FVIII product is estimated using time points from 1h to 30h, while for N8-GP is estimated using time points from 6h to 96h. Patient [redacted] was excluded from the analysis. Patient [redacted] was excluded from the t½ calculation for N8-GP. The analysis is based on a mixed model with patient as a random effect. CV: Coefficient of variation, CI: Confidence Interval, AUC: Area under the curve, CL: Clearance. Chromogenic NHP Assay used for Previous FVIII treatment

Figure 2**:** shows mean profiles of FVIII activity after a nominal dose of 50 U/kg (N8-GP) and 50 IU/kg (previous FVIII product). In both age-groups, a higher peak FVIII activity level and a prolonged plasma half-life (t½) was observed for N8-GP compared to previous FVIII product.

Mean (range) PK doses for previous product were 48.3 (20.0-55.0) for the 0-5 year age-group and 46.4 (29.0-60.0) for the 6-11 year age-group. Mean (range) PK doses for N8-GP were 55.4 (50.2-60.7) for the 0-5 year age-group and 53.8 (30.9-66.9) for the 6-11 year age-group.

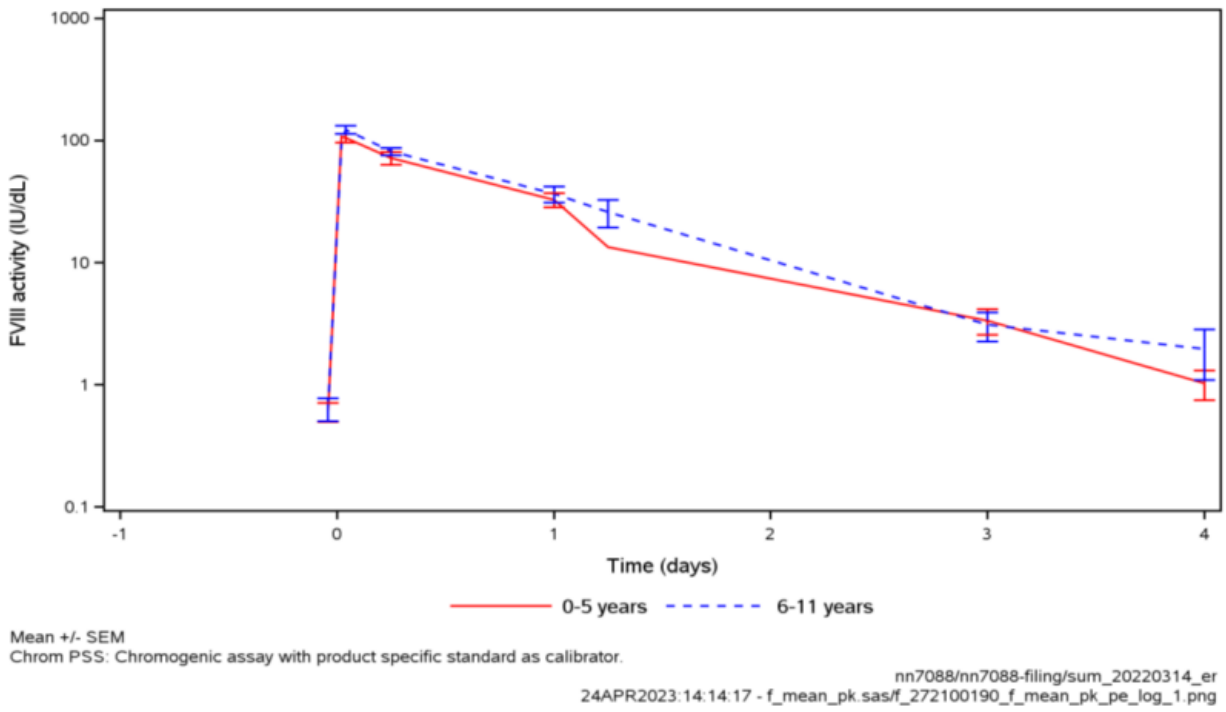
Using the population-based method, estimates of t½ were 7.4 hours for previous FVIII product compared with 13.9 hours for N8-GP. The half-life of N8-GP was 1.9 times longer than that of the patients' previous FVIII products.

Figure 2: Mean FVIII activity profiles of N8-GP and previous FVIII product



According to the Applicant, the specific data point in the 0-5 years subgroup at 30h is based on a single observation (n=1).

Figure 3: Mean single-dose pharmacokinetic profiles of FVIII activity (IU/dL) (log scale) - age < 12 years old – 50 IU/kg – trial 3885 – chrom PSS – full analysis set



FVIII activity: pre and post dose

FVIII activity levels were assessed pre-dose (trough) and 30 minutes post-dose. The assessments were performed without a wash-out period. Analysis of FVIII trough showed that the mean trough level was 0.016 IU/mL in children 0-5 years of age and 0.024 IU/mL in children 6-11 years of age.

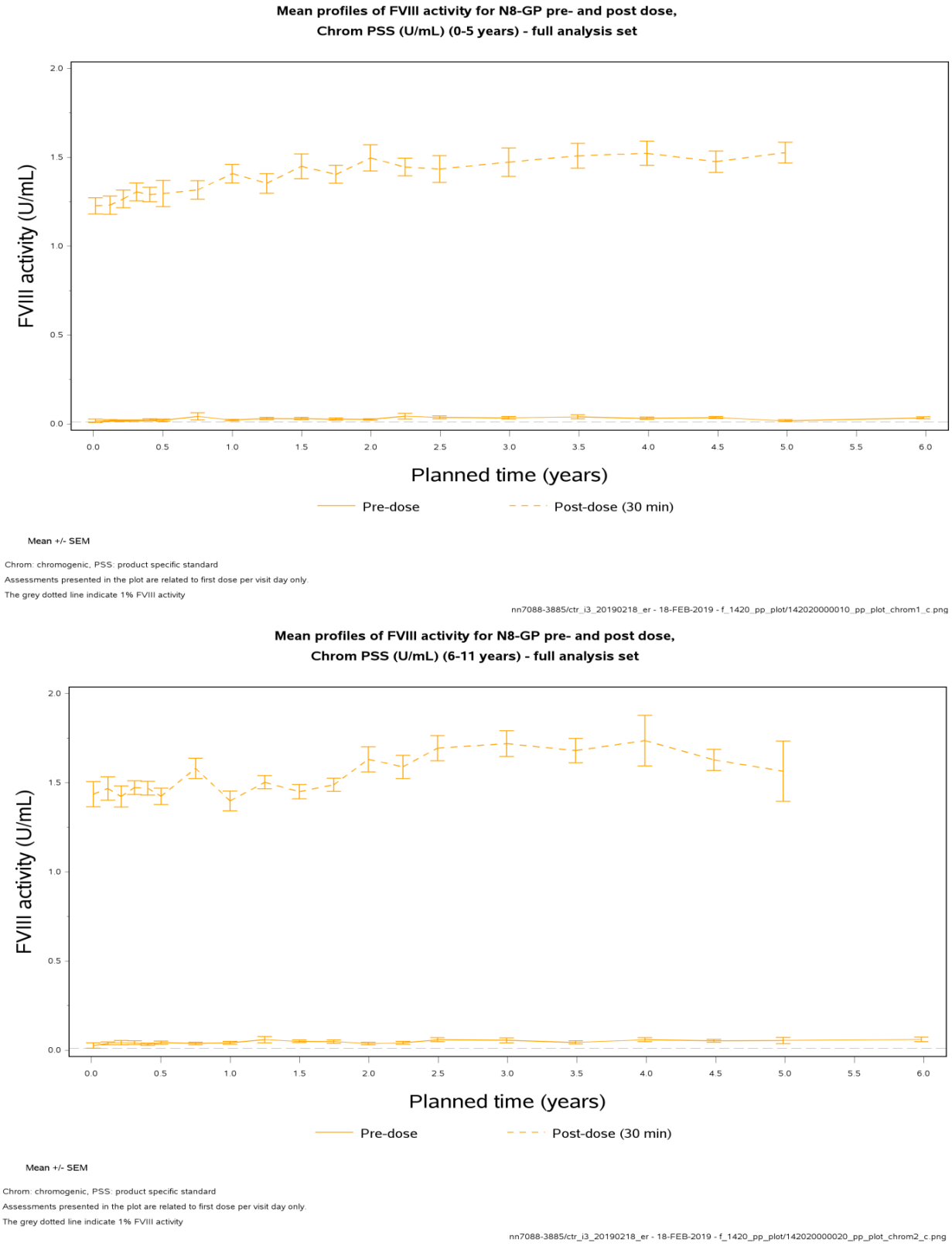
Table 3: FVIII trough analysis (chromogenic PSS) – full analysis set

	Younger children (0 - 5 years)	Older children (6 - 11 years)	Total
Number of patients	34	34	68
Number of trough values included in the analysis	490	585	1075
Number of trough values excluded from the analysis	37	32	69
Number of values below lower limit of quantification*	164	132	296
Mixed model results**			
Mean trough level (IU/mL)	0.016	0.024	0.019
95% CI	0.012 ; 0.021	0.018 ; 0.031	0.016 ; 0.024

CI: Confidence interval
* Plasma activities below lower limit of quantification (LLOQ) are set to half of LLOQ.
** Mixed model on the log-transformed plasma activities with age group as fixed effect and patient as a random effect.
Chromogenic assay with product specific calibrator was used.
Pre-dose values are excluded if: the post-dose value <= the pre-dose value;
Pre-dose sample is taken < 7 days since the last dose related to surgery or treated bleed;
Pre-dose sample is taken < 1.5 days or > 5.5 days since last dose.

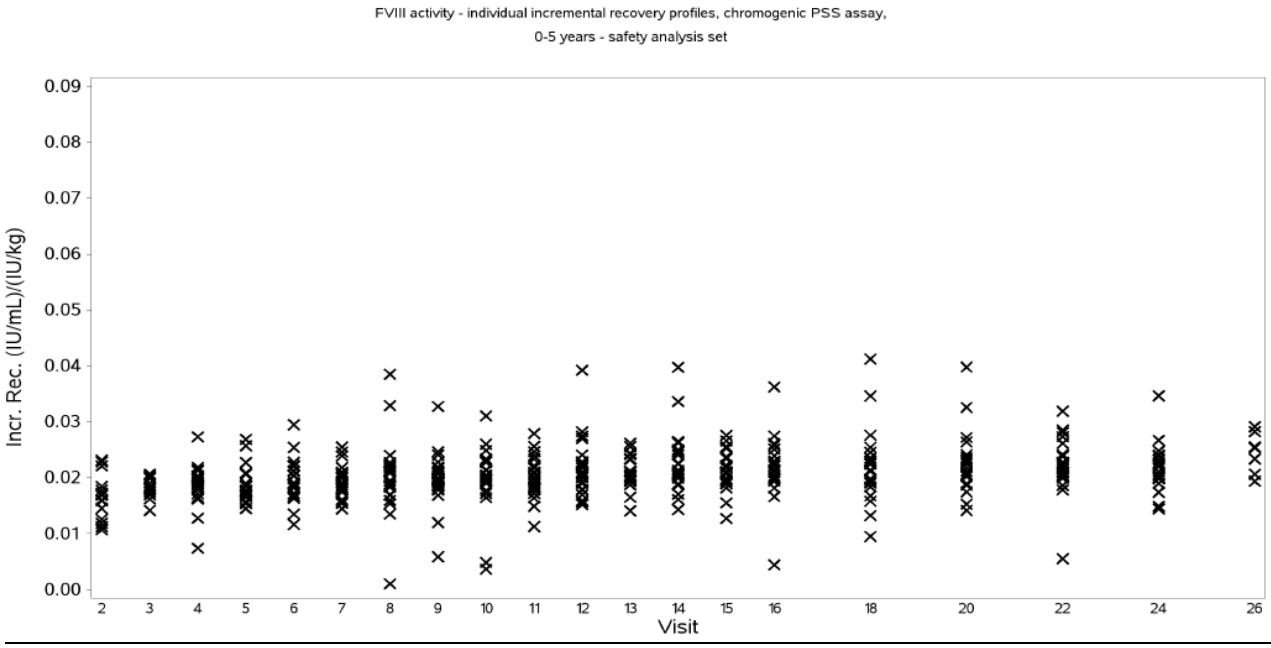
In trial 3885 in PTPs, mean trough levels for the 0-5 years age-group were 0.016 IU/mL (0.012; 0.022)95% CI and 0.024 IU/mL (0.018; 0.031)95% CI for the 6-11 years age-group. Not all patients had measurable FVIII activity pre-dosing. In all, the number of values below the lower limit of quantification (LLOQ) was 164 out of 490 (33.47%) for the 0-5 years age-group and 132 out of 585 (22.56%) for the 6-11 years age-group, indicating a higher clearance in the 0-5 years age-group.

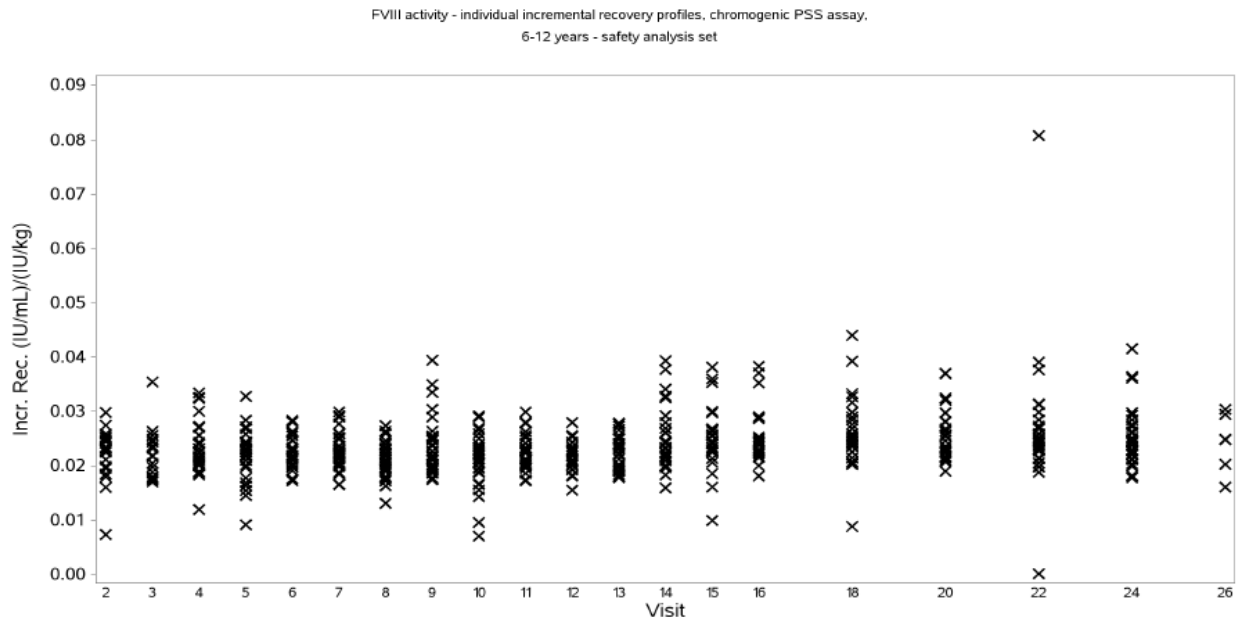
Figure 4: Mean pre- and post-dose FVIII activity of N8-GP by time in trial (chrom PSS)



FVIII activity (0–5 year age group on the top and 6–11 year age group bottom) (mean±SEM) was assessed by the chromogenic assay using product specific standard as calibrator. Grey dotted line at the bottom indicates 1% FVIII activity level. The last data point for patients in the 6–11 year age group was caused by data from a single patient who had an outlying high FVIII activity level.

Figure 5: FVIII activity - Incremental recovery profiles in PTPs (30 minutes post-dose)





Incremental recovery profiles (IR_{60min}) were slightly lower in the 0-5 year age group (0.018 IU/mL/IU/kg) than in the 6-11 year age-group (0.020 IU/mL/IU/kg).

Figure 6: Predicted FVIII activity levels at steady state - ≤ 12 years

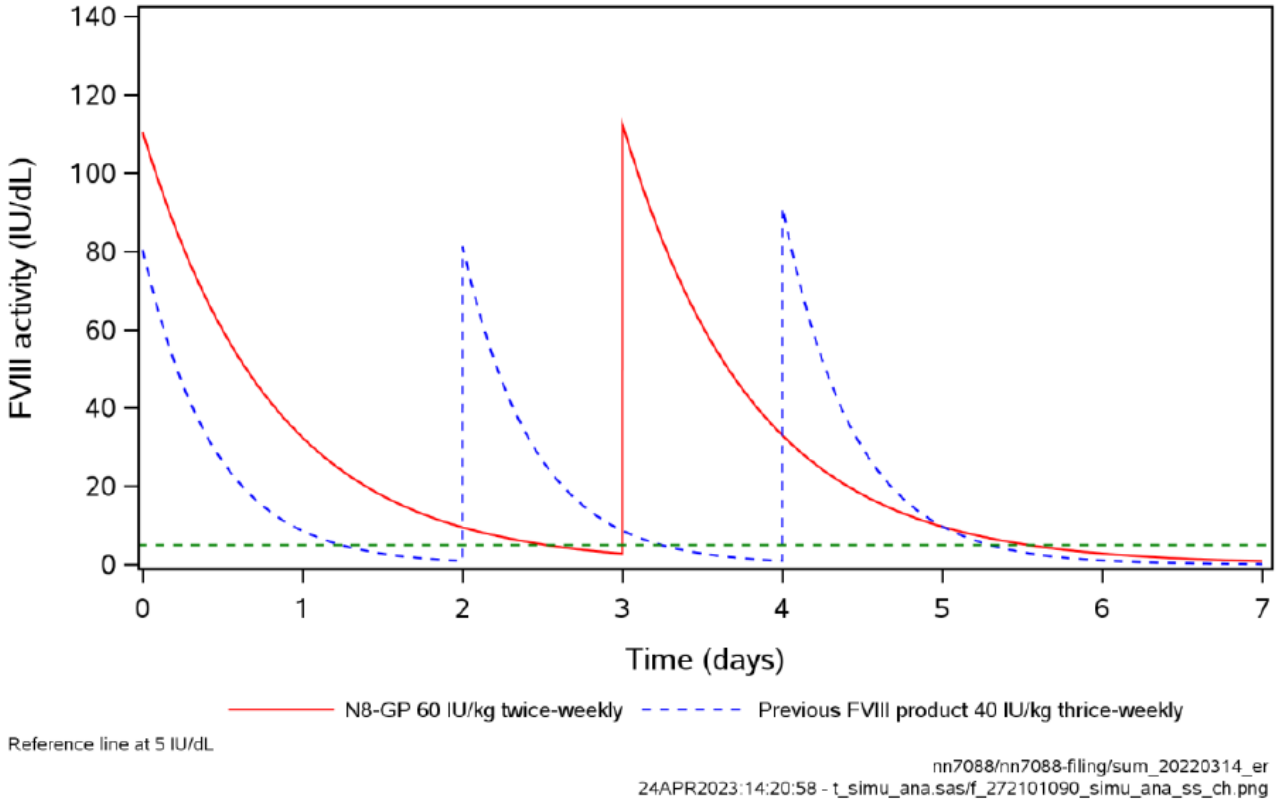
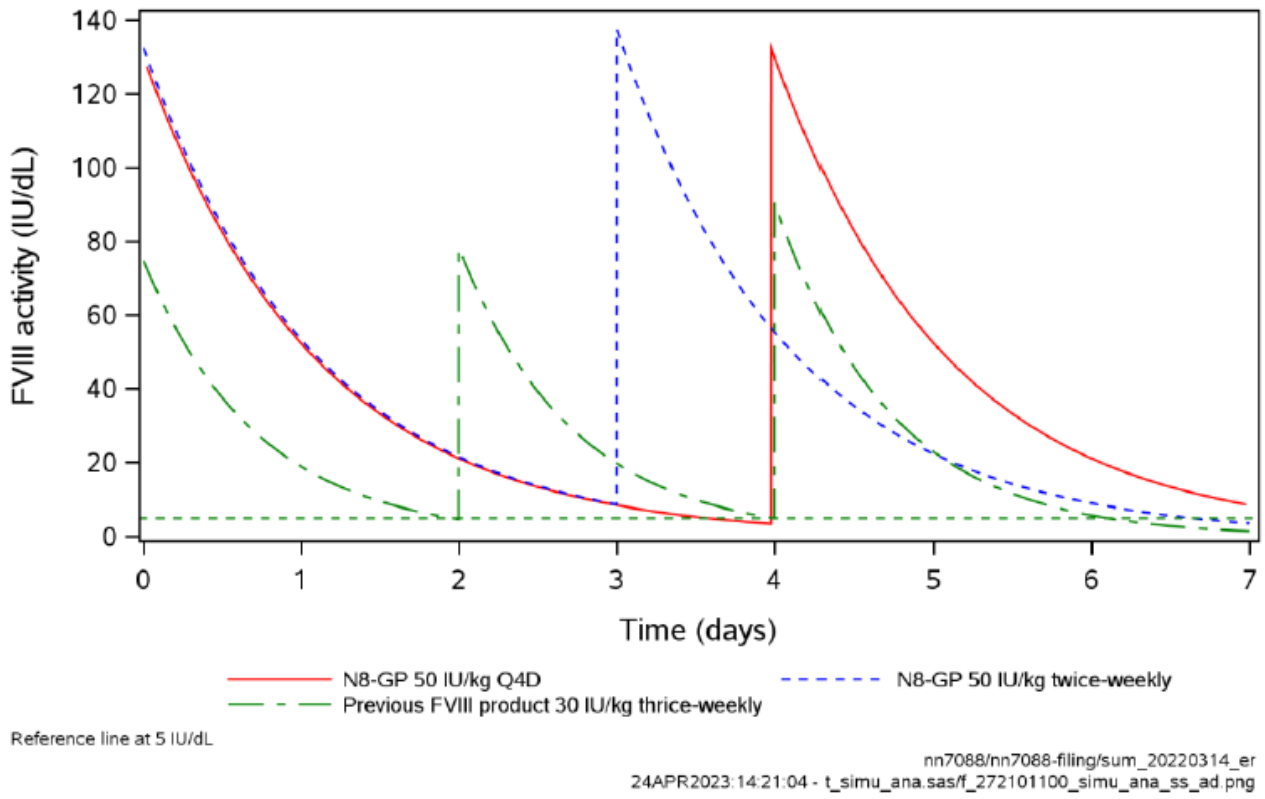


Figure 7: Predicted FVIII activity levels at steady state - age ≥ 12 years



Trial NN7088-3908:

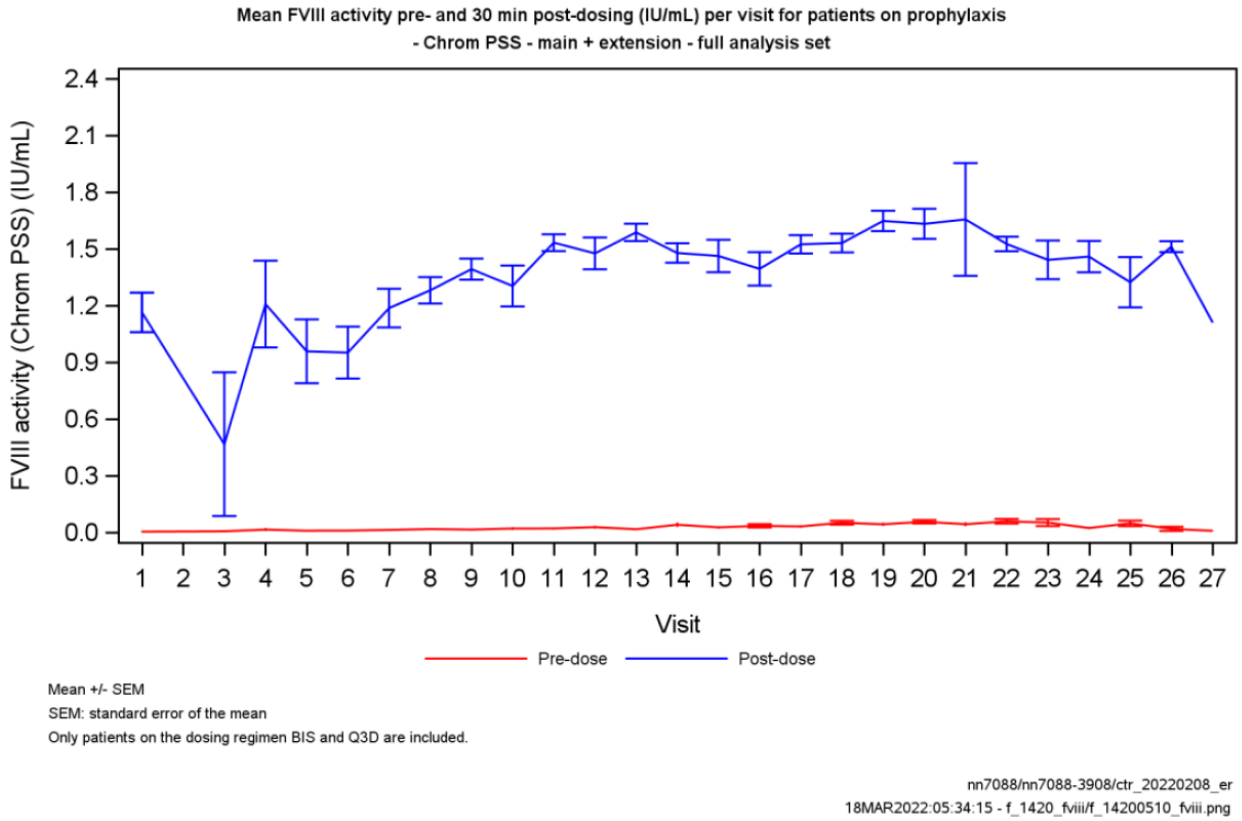
FVIII activity

Mean FVIII activity (IU/mL) at pre-dose and at 30 min post-dose, obtained with the chromogenic assay with PSS as calibrator, is presented by visit in Figure 8**:** for patients on twice weekly or every 3rd day prophylaxis regimen.

FVIII activities in pre-dose samples (i.e., FVIII trough levels) were as expected due to the relatively high clearance of N8-GP in young children. A statistical analysis (mixed model) of pre-dose samples at prophylaxis showed a mean FVIII activity trough level of 0.015 IU/mL (95% CI: 0.011 ; 0.019) (Table 14.2.78). Of the 355 samples included in the analysis, 128 measurements were below the lower limit of quantification (LLoQ) of 0.009 IU/mL and were set to half of the lower limit of quantification, i.e., 0.0045 IU/mL.

The FVIII activity 30 min post dosing at visit 3, which corresponds to 5 EDs, was lower than expected for some patients and is discussed below.

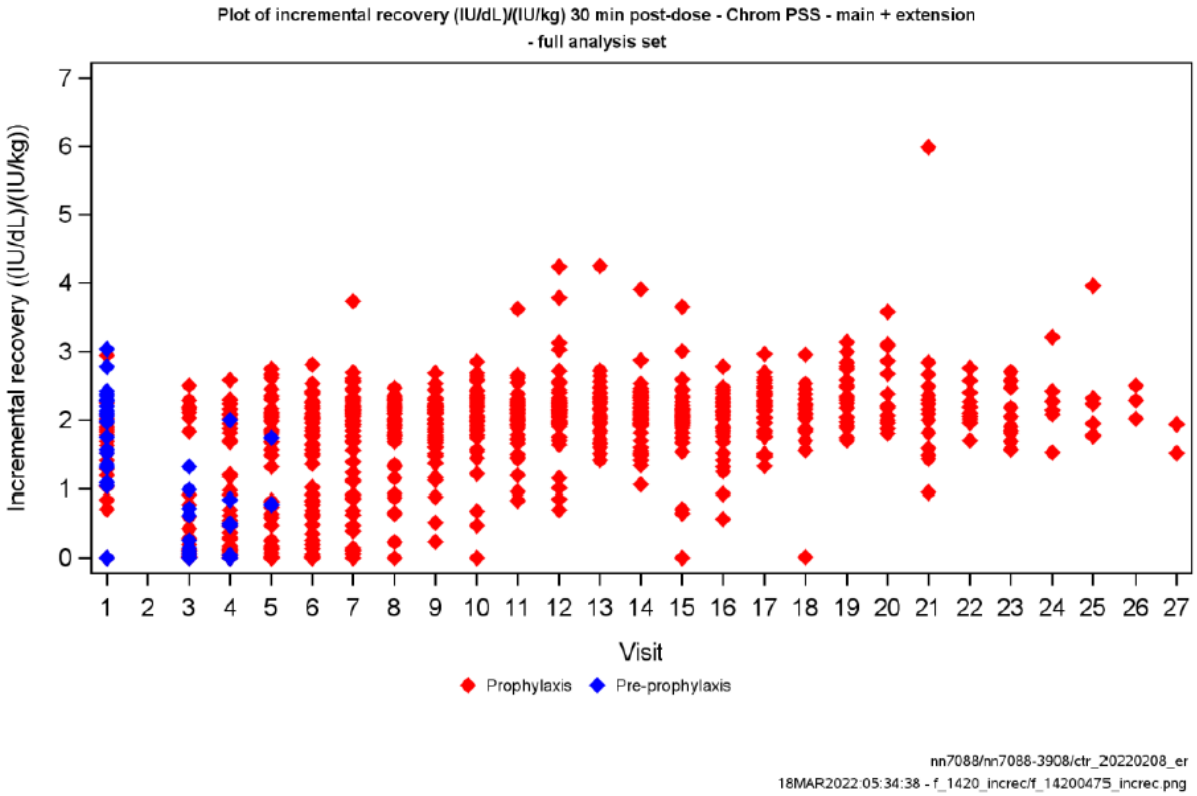
Figure 8: Profiles of mean FVIII activity (IU/mL) at pre-dose and at 30 min post-dose by



Incremental recovery

Incremental recovery (IR) is defined as the increase in plasma FVIII activity per IU/kg of N8-GP administered and is expressed in (IU/dL)/(IU/kg). Individual values of IR at 30 min post-dose by visit for patients on pre-prophylaxis or prophylaxis are presented in Figure 9. Most IR values were between ~1.5 to ~2.5 (IU/dL)/(IU/kg), which is as expected based on previous observations of N8-GP in previously treated patients (PTPs) of similar age (trial NN7088-3885).

Figure 9: Plot of individual values of IR [(IU/dL)/(IU/kg)] at 30 min post-dose by visit



Low IR was defined as an IR <0.6 (IU/dL)/(IU/kg). This definition was based on the lowest IR value observed in previously treated paediatric patients of the same age (i.e., <6 years), receiving 60 IU/kg twice weekly prophylaxis during the main phase of trial NN7088-3885. Thus, 0.6 (IU/dL)/(IU/kg) was to be considered by the Applicant the best cut-point for specifying what a decreased IR value should be. A period of decreased IR in a patient was defined as the period from the last visit before the patient had the first decreased IR measurement until IR was again ≥0.6 (IU/dL)/(IU/kg).

A total of 59 non-inhibitor patients (i.e., absence of FVIII inhibitors) were included in these assessments. Three sub-populations were defined from the 59 non-inhibitor patients:

*Non-inhibitor patients with no measurements of decreased IR (**N=28/59 non-inhibitor patients**):* These patients had no decreased IR measurements (i.e., no observations of IR <0.6 (IU/dL)/(IU/kg)). Patients with missing measurements of IR were included, as were patients who withdrew before 10 EDs.

*Non-inhibitor patients with single measurement(s) of decreased IR (**N= 14/59 non-inhibitor patients***): These patients had one single observation of decreased IR, but no consecutive observations of decreased IR.

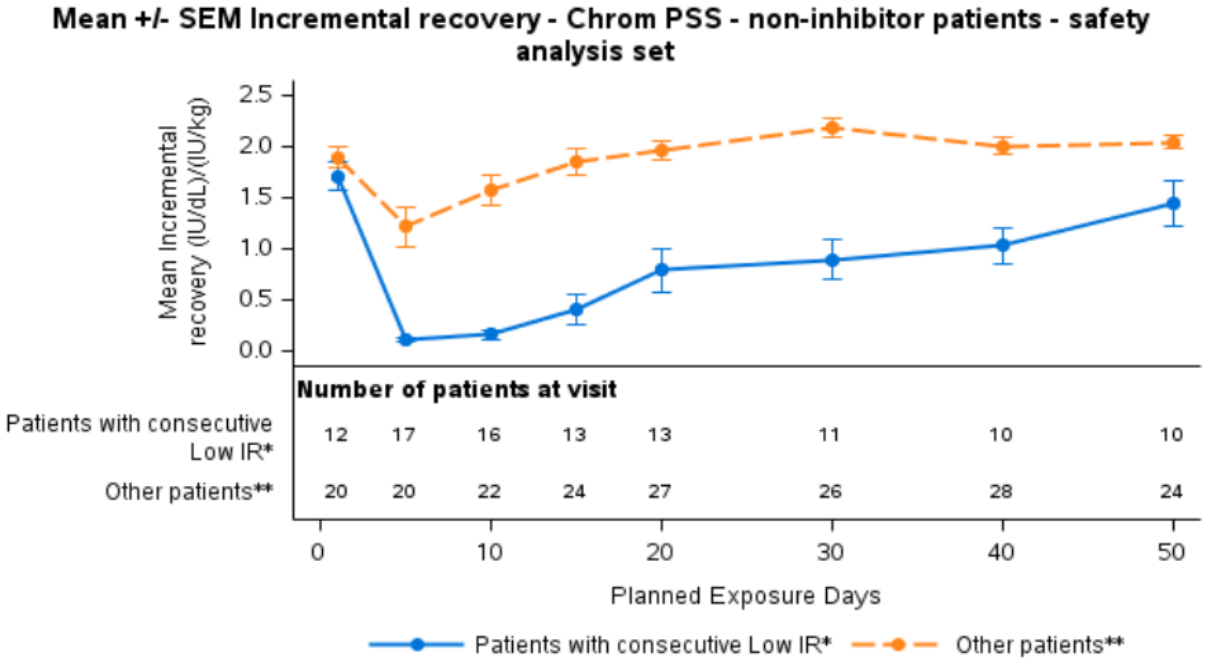
*Non-inhibitor patients with consecutive decreased IR (**N=17/59 non-inhibitor patients**):* These patients have at least 2 consecutive observations of decreased IR.

The 17 patients with a consecutive decrease in IR were on average approximately twice as old as the 42 'other' patients at first dose in the trial (17.2 vs 9.2 months). No data was provided for patients with single measurements of decreased IR.

A decrease in IR for the patients with consecutive decreased IR was observed during initial exposures to N8-GP (EDs 5 and 10), followed by a normalisation of the IR (i.e., ≥0.6 (IU/dL)/(IU/kg)) after continued dosing.

A decrease is also seen in the mean profile for the 42 'other' patients. As patients with single decreased IR measurement are included in this patient group, the observation is likely due to single decreased IR values in these patients.

Figure 10: Trial 3908: Profiles of IR (mean±SEM) [(IU/dL)/(IU/kg)] for patients with consecutive decreased IR (N=17) and 'other' (N=42) non-inhibitor patients – chrom PSS – safety analysis set



From Visit 1 to Visit 9.

*Patients with at least two consecutive observations of incremental recovery below 0.6 [IU/dL]/[IU/kg].

**Patients with non-consecutive or no low values of incremental recovery.

Patients with positive inhibitor tests at either screening or baseline visits are excluded from this output.

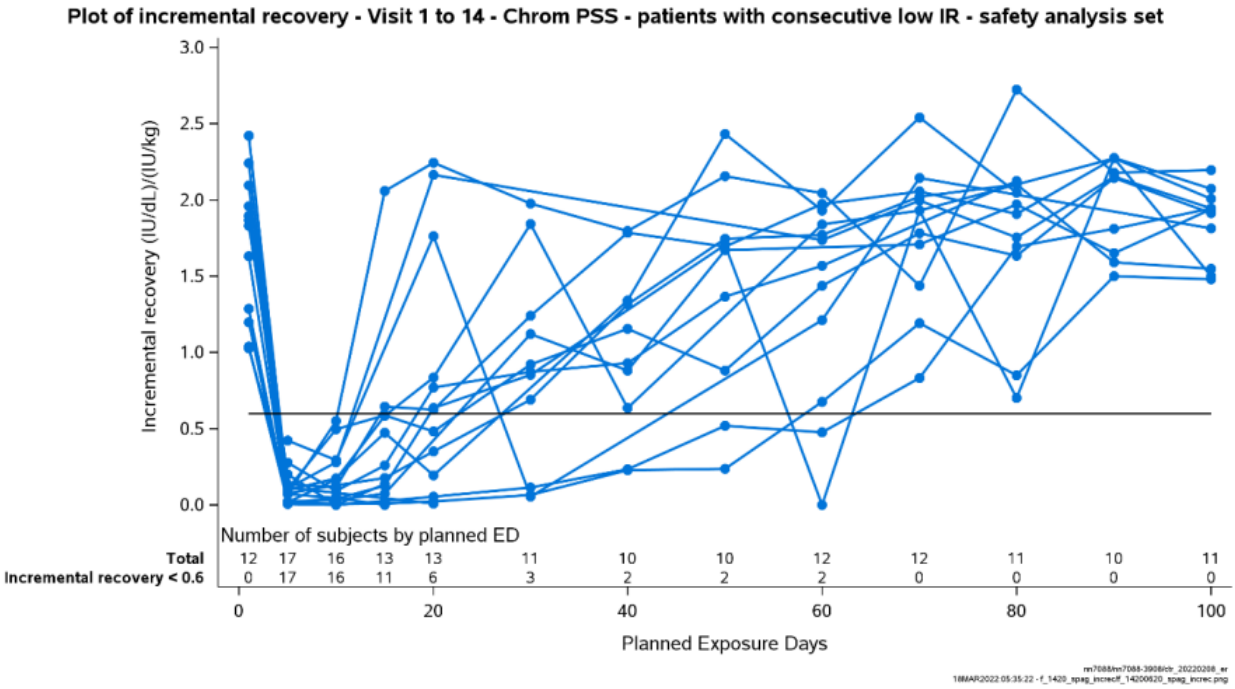
Individual profiles of IR in non-inhibitor patients with consecutive decreased IR (N=17)

At the first measurement (corresponding to the first exposure to N8-GP), all patients had IR values within normal range. At EDs 5 and 10, all IR values for all 17 patients were below 0.6 (IU/dL)/(IU/kg).

At 20 EDs of continued dosing, 7 of the 17 patients had returned to IR ≥0.6 (IU/dL)/(IU/kg) while 6 patients still had IR below 0.6 (IU/dL)/(IU/kg) and 4 patients had withdrawn from the study. At 70 EDs, all remaining patients had returned to normal IR levels ≥0.6 (IU/dL)/(IU/kg).

4 patients withdrew from the study due to low IR at 14, 17, 19, and 10 EDs.

Figure 11: Trial 3908: Individual profiles of IR - Visits 1 to 14 - Chrom PSS – non-inhibitor patients with consecutive decreased IR – safety analysis set



Root cause analysis

There were no clinically relevant differences in country of origin, ethnicity or race. The 17 patients with a low IR were on average approximately twice as old as the 42 'other patients' at first dose in the trial (17.2 vs 9.2 months). Reported bleeding frequency was comparable between low-IR patients and 'other patients': There were no clinically relevant differences in adverse event rates or types of adverse events reported between low-IR patients and remaining patients.

The proportion of patients who developed anti-drug antibodies was higher for low-IR patients compared to the 'other patients'; 64.7% vs. 26.2% for anti-FVIII antibodies, 70.6% vs. 61.9% for anti-PEG IgG antibodies, respectively. There were 53.0% low IR patients vs. 14.3% 'other patients' who developed anti-PEG IgM antibodies. These findings were consistent with an increased immune response in non-inhibitor low IR patients across the three analysed antibodies. In patients with consecutive decreased IR, a transient increase of anti-PEG IgG with peak levels at ED 5 (Visit 3) was observed, followed by a gradual decrease in antibody levels.

Statistically significant associations between IR and each of the 3 antibodies were found.

Table 4: Mixed model incremental recovery vs. titre – non-inhibitor patients

Antibody	p-value
Anti-PEG IgG	<0.0001
Anti-PEG IgM	0.0327
Anti-N8-GP	<0.0001

Incremental recovery is analysed using a multivariate linear regression, with covariates: logarithm of Anti-N8-GP, logarithm of Anti-PEG IgG, and logarithm of Anti-PEG IgM titers. The estimation also accounts for subject random effects.

Negative antibody results have an imputed titer of 0.1 for Anti-N8-GP and Anti-PEG IgG, and 0.05 for Anti-PEG IgM.

2.3.3. Pharmacodynamics

The PK parameters of N8-GP were based on plasma FVIII activity. This parameter is known to correlate with clinical efficacy of FVIII products. Thus, the plasma FVIII activity is to be considered pharmacodynamic in nature, as it reflects the biologic action of N8-GP. No other pharmacodynamic endpoints have been assessed in the clinical development programme for N8-GP.

2.3.4. Discussion on clinical pharmacology

Trial 3885 in paediatric PTPs

Pharmacokinetic data of Esperoct in paediatric PTPs ≤12 years of age with severe haemophlia A (FVIII levels <1 %) were derived from study 3885. The chosen PK parameters as well as number of patients fulfil the requirements as outlined in the guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009 rev. 2).

Of note, data are presented using a chromogenic or clotting assay, with either NHP or PSS as calibrator. The analysis plan specified that a chromogenic and clotting assay with PSS calibrator will be used. Already during prior assessment rounds (see EPAR) the Applicant has clarified that the chromogenic assay with PSS as calibrator has turned out to be the most suitable assays/calibrator combination, which is also in line with the recommendation from the scientific guideline (EMA/CHMP/BPWP/144533/2009 rev. 2). Thus, results from this assay-calibrator combination will be referred to in this assessment (as results for PK parameters differ depending on the assay and calibrator used) if not specifically stated otherwise. The PK profile of the previously utilised FVIII product was also investigated for a subset of PTPs. However, data were acquired with the chromogenic assay using normal human plasma (NHP) as calibrator whereas data for Esperoct are presented using the PSS as calibrator, which masks any comparison of PK parameters between products unsuitable as the change in calibrator is confounding the interpretation. Furthermore, different time points were utilised for the calculation of t1/2, (1-30h for the previous product and 6-96h for Esperoct) and different previous FVIII products were used, which renders the estimation and comparison of half-life unprecise.

Single-dose PK data are reported for 4 days after infusion of 50 IU/kg for 27 children (40% of children enrolled in study 3885), 15 PTPs 0-5 years and 12 children 6-11 years, and concluded a mean t1/2 of 13.9h and 14.6h, respectively. The mildly shorter $t^{1/2}$ in younger children is in line with the expected mildly higher clearance rate (2.6 mL/h/kg and 2.4 mL/h/kg, respectively). Notably, the dose used for the single-dose PK is the lowest possible dose intended for licensure (50-75 IU/kg). During study 3885 a dose of 60 IU/kg was recommended and a mean/median prophylactic dose of 65.4/66.5 and 64.1/64 IU/kg in PTPs 0-5 and 6-11 years was actually used as per reported consumption data, respectively.

Including extension data from study 3885 the MAH provides data on Factor VIII trough levels measured from pre-dose samples up to 6 years after treatment initiation. Of note, in contrast to the single-dose PK data reported above, data for repeat dose PK are based on the actually used doses (around 64 IU/kg, see above). Mean trough levels of 0.016 and 0.024 IU/mL were concluded for 0-5 years old and 6-11 years old PTPs, respectively, which is within the range of moderate haemophilia A (0.01-0.05 IU/ml). Lower levels in the age group 0-5 years are expected considering the higher clearance rate in this age group.

However, a large number of trough level measurements of N8-GP were below 0.01 IU/mL, which corresponds to a FVIII activity of 1% or the upper limit of a Haemophilia A status of 'severe'. Prior to dosing, 164/490 (33.5%) and 132/585 (22.6%) FVIII trough measurements were below LLOQ (0.009 IU/mL) in the 0-5 and 6-11 years groups, respectively. Values below LLOQ were set to half LLOQ (0.005 IU/mL). In the original CTR median FVIII trough levels were reported as 0.005 IU/mL in both the 0-5 and 6-11 year groups, indicating that (1) a large number of values were imputed and (2) that relatively high

trough levels in few patients skewed the data. No median trough values were reported in this submission. The applied imputation strategy of data LLOQ might over- or underestimate true trough levels. The Applicant provided mean and median FVIII trough levels with alternative imputation strategies for samples LLOQ. Data measured as LLOQ were set to either 0.008 (the limit for the chromogenic PSS combination is <0.009) or to 0.00001 IU/mL (worst case assumption considering the required log transformation to derive estimates). As expected, mean values are slightly lower for the imputation with minimum value compared to the imputation with maximum value below LLOQ. However, differences are not substantial and median values do not differ between both imputation strategies. In any case, considering the amount of data below LLOQ, a large proportion of subjects will spend pre-dose times with Factor VIII levels in the severe haemophilia A range, which is de facto an untreated level. The exact time these subjects spent with a Factor VIII level below 1% is unclear. In trial 3776 in adult PTPs the mean duration from dosing to a plasma activity of 1% was 6.6 days. A twice weekly dosing regimen was chosen to ensure >5% FVIII activity almost throughout the entire 7-day dosing window. Based on modelled predictions of plasma FVIII activity at steady state 90% of the dose interval (following the recommended 4 day schedule) should be spent above 5% for patients ≥12years. Paediatric subjects are predicted to spend less time above this threshold during their dosing interval twice weekly, with either 84.6% or 72.3% of the time when following either the schedule every three days or every 4 days, respectively, even with the 20% increase in dose per kg bodyweight (60 IU/kg). Upon request, the dose depicted in the PI was elevated to 65 IU/kg (from initial 60 IU/kg) and a possible range from 50-75 IU/kg is depicted. It is acknowledged that patients are in close observation by their treating physicians and that starting doses as well as dose adjustments are set on an individual basis. Patients were administered Esperoct twice weekly during the study, which is also the recommended dosing schedule in the PI. Based on available PK data on trough levels, shorter treatment intervals could be necessary as is also reflected by recommendations provided in the PI (see section 4.2). Importantly, the mean post dose Factor VIII levels (30 minutes) were between 1-1.5 IU/mL for PTPs 0-5 years old and around 1.5 IU/mL for PTPs 6-11 years old, throughout the observation period (i.e. 5 years). The mean incremental recovery 30 minutes post-dose was >0.02 (IU/dL)/(IU/kg) throughout all visits for PTPs 6-11 years old. Min-max values also indicate that no measurement was below 0.006 (IU/dL)/(IU/kg) in this age group (all referring to the chromogenic assay with PSS). Mean IR values in PTPS 0-5 years old were ≥ 0.017 (IU/dL)/(IU/kg), but min-max values as well as graphically depicted data indicate a few measures ≤0.006 (IU/dL)/(IU/kg) (e.g. visit 8, 9, 10, 16 and 22). However, after assessment of these patients no specific concern appears associate to the few measures of low IR in PTPs.

Trial 3908 in paediatric PUPs

Pharmacology as well as clinical efficacy and safety data have been assessed in detail during a past variation procedure already. Reference is made to the type II variation procedure EMEA/H/C/004883/II/0013 with final Opinion on February 2023 (see EPAR EMA/125435/2023). However, in the referred variation procedure changes to the PI were sought, whereas in the current procedure the label extension to paediatric patients is requested.

Pharmacokinetics after single exposure was not evaluated for PUPs. Pharmacokinetic assessments included FVIII activity pre-dose (trough), 30 minutes post-dose, and incremental recovery expressed in (IU/dL)/(IU/kg). Measurements were made in a subset of patients of varying size at each visit (in total n=59 patients provided samples for pharmacology and n=30-40 samples were available for each visit). Mean FVIII activity level pre-dose was 0.015 IU/mL, with 36.1% (128/355) of measurements included in this analysis resulting in values below LLOQ. These data are principally comparable to reported levels in PTPs of the same age group (0.016 IU/mL with 3.5% of samples below LLOQ). Thus, more than one third of samples indicate Factor VIII levels in the range of severe haemophilia. The handling of LLOQ samples was not pre-specified in the analysis plan. Upon request, the Applicant provided mean and median FVIII trough levels with alternative imputation strategies for samples LLOQ. Data measured as LLOQ were set

to either 0.008 (the limit for the chromogenic PSS combination is <0.009) or to 0.00001 IU/mL (worst case assumption considering the required log transformation to derive estimates).

Of note, the mean/median consumption of PUPs during trial 3905 was 68.9/69 IU/kg, which indicates that the recommended study dose of 60 IU/kg does not fulfil the actual requirements of PUPs. Upon request, the MAH has amended the starting dose recommendation to 65 IU/kg (range from 50-75 IU/kg), which is closer to the actually observed consumption and in line with the recommendation for paediatric PTPs. It is also acknowledged that patients are in close observation by their treating physicians and that starting doses as well as dose adjustments are set on an individual basis.

Post-dose FVIII activity measurements in this patient group showed reduced activity in a large proportion of participants, falling from a mean 1.203 IU/mL at visit 1, to a mean of 0.393 IU/mL at visit 3 (roughly 5 ED). Levels continuously rose over the next visits until roughly stabilising at visit 11 (roughly 70 EDs) a level of 1.5 IU/mL. As a consequence of these low post-dose values, a large proportion of PUPs had low values for IR (i.e. <0.6 (IU/dL)/(IU/kg)) reported, as also extensively discussed in the prior variation procedure. It is reiterated that of those patients who did not develop inhibitors (59 of 81 included PUPs) 17 patients were observed with consecutive low IRs and further 14 patients had a single measure of low IR, whereas 28 subjects did not have any measure of decreased IR. These numbers indicate that the majority of the PUPs without inhibitors had at least one measure of a decreased IR, with particular frequent observations during the early phase of the trial. Low IR was observed especially within the first 30 ED (76.9% of subjects with low IR were back to normal IR within 30 EDs), but lasted up to ED 60, which is in line with the reduced mean post-dose Factor VIII levels described above. A root cause analysis concluded a possible association to anti-drug antibodies (especially PEG-IgG, and less evident for PEG-IgM and anit-N8-GP), which is principally a plausible explanation for the drop in IR in some PUPs.

Upon request, the MAH provided an overview on clinical outcomes for all non-inhibitor patients with temporary decreased IR during the period of low IR and for patients with normal IR during the entire treatment period. For the provided overview, the Applicant lists n=42 PUPs with "normal IR during the entire study period". This depiction is questionable, as additional n=14 PUPs without inhibitors also had a single measure of low IR, which would rather result in n=28 PUPs with normal IR during the entire study period. However, it is acknowledged that no time period can be attributed to a single measure. Thus, the depiction appears as a reasonable way forward. Of the 17 patients with consecutively reduced IR (of in total 59 PUPs without inhibitors), 4 patients have discontinued the trial and 13 patients continued the treatment with N8-GP during the period of low IR. The time of low IR started around 5-10 EDs after treatment initiation and returned back to normal IR within 70 EDs. The majority of patients had returned back to normal IR within 30 EDs (76.9%). The proportion of subjects with bleeds was higher in the group with low IR during the time of low IR (n=14 of 17 patients, 82.4%) compared to the proportion of subjects with bleeds in the group with normal IR during the entire study period (n=28 of 42 patients, 66.7%). The rate of spontaneous bleeding events was slightly higher in subjects with low IR during the time of low IR (23.3% of all bleeds) compared to those with normal IR during the entire study period (18.1% of all bleeds), but absolute numbers are low (n=7 and 23 spontaneous bleeds, respectively). Notably, the rate of severe bleeds was substantially higher in patients with low IR during the period of low IR (16.67%) compared to those with normal IR (0.5%). Again, absolute numbers are low (n=5 and 1 severe bleeds, respectively) and only 1 of the severe bleeds in PUPs with low IR was a spontaneous bleed. All but one of the 5 severe bleeds were successfully treated with on-demand doses, resulting in a slightly reduced success rate for subjects with low IR of 83.2% compared to 93.6% (91.2% when including missing as failure) in PUPs with normal IR. These data indicate a potentially reduced efficacy in PUPs with low IR. The respective warning in section 4.4. highlights that "*Consecutive low IR could potentially be associated with reduced efficacy during this time period*" and that discontinuation of the product should be considered in case of unsatisfying bleeding control with Esperoct. The amended warning in section 4.4. is agreed to stress the risk of low IR in PUPs including the risk of reduced efficacy

as well as the need to monitor patients and implement necessary steps in case bleeding control is not warranted.

Notably, this finding was not mirrored in paediatric PTPs in trial 3885, during which subjects in the 0-5 year age group who were anti-PEG negative prior to treatment showed neither tendency for decreased IR, nor development of anti-PEG antibodies (1/17 patients 0-5 of age developed transient anti-PEG antibodies). Patients who were anti-PEG positive prior to treatment also did not have low IR measurements. As mentioned briefly above, it is suspected that PEG IgG antibodies are associated to the decreased IR in PUPs. T-cell activation is speculated to be required for the induction of anti-PEG IgG antibodies, which is not expected in PTPs based on previous exposure to FVIII products (and an expected tolerance to external FVIII including N8-GP). The titer of pre-existing PEG IgM antibodies were low with expected low affinity to N8-GP. The explanation provided by the MAH can be followed.

In conclusion, although efficacy results in the general trial population were principally not concerning (see discussion on efficacy), a large subset of PUPs who did not develop inhibitory antibodies responded to primary exposure of Esperoct with a period of low IR of varying length that was associated with a potentially reduced efficacy during the time of low IR compared to other patients without consecutively low IR. Consecutive measurements of low IR were association with anti-PEG IgG antibodies. While the phase with low IR was self-limited for the affected patients, the duration of up to 60 EDs is of concern. The respective warning statement on potentially low IR in PUPs in the SmPC is acknowledged.

2.3.5. Conclusion on clinical pharmacology

Mean trough Factor VIII levels are relatively low, despite the adjusted dosing recommendation for paediatric patients during both studies (60 IU/kg instead of 50 IU/kg in subjects ≥12 years) and the additionally adjusted dosing as applied in the younger paediatric groups (a mean of 65.4 and 64.1 IU/kg in PTPs 0-5 and 6-11 years and 68.9 IU/kg in PUPs); but in average, the levels were above the threshold for severe Haemophilia A. As a consequence, the dosing recommendation in the PI was amended to 65 IU/kg (50-75 IU/kg) administered twice weekly for paediatric patients. Results on mean FVIII trough levels based on different imputation strategies require further exploration.

Importantly, a large proportion of PUPs with consecutively low IR, that was associated with an increase in severe bleeds as well as a lower haemostatic response is concerning and warrants the included warning statement in section 4.4. of the SmPC on decreased factor VIII incremental recovery in previously untreated patients.

2.4. Clinical efficacy

2.4.1. Main studies

Trial ID: NN7088-3885: A Multinational, Open-Label, Non-Controlled Trial on Safety, Efficacy and Pharmacokinetics of NNC 0129-0000-1003 in Previously Treated Paediatric Patients with Severe Haemophilia A

Phase 3 multi-national, open-label, single-arm, and non-controlled trial to assess safety including immunogenicity, efficacy and PK of N8-GP. The trial product was given for prophylaxis and treatment of bleeding episodes to patients below 12 years of age with severe haemophilia A.

Trial ID: NN7088-4410: Safety and Efficacy of turoctocog alfa pegol (N8-GP) in Prophylaxis and Treatment of Bleeds in Previously N8-GP Treated Patients with Severe Haemophilia A

Phase 3b, multi-centre, multinational, open-label, non-randomised, interventional trial investigating safety and efficacy of N8-GP in prophylaxis and treatment of bleeding episodes in previously N8-GP treated severe haemophilia A patients of all age groups (pathfinder8). The trial included three N8-GP treatment arms and no comparator.

Trial ID: NN7088-3908: Safety and Efficacy of turoctocog alfa pegol (N8-GP) in Previously Untreated Patients with Haemophilia A

An open-label single-arm multicentre non-controlled phase 3a trial investigating safety and efficacy of N8-GP in prophylaxis and treatment of bleeding episodes in previously untreated paediatric patients with severe haemophilia A.

Methods

Study participants

Trial ID: NN7088-3885

Inclusion criteria

For an eligible patient, all inclusion criteria had to be answered "yes".

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Male patients with severe congenital haemophilia A (FVIII activity level < 1%, according to medical records)
3. Age below 12 years at screening (for Turkey only: age above 3 and below 12 years at screening)
4. Weight ≥10 kg at screening
5. Documented history of > 150 EDs to FVIII products for patients aged 6-11 years and > 50 EDs to FVIII products for patients aged 0-5 years (for Turkey only: Documented history of > 150 EDs to FVIII products for patients aged 6-11 years and > 50 EDs to FVIII products for patients aged 3-5 years)
6. The patient and/or parent(s)/caregiver are capable of assessing a bleeding episode, keeping an electronic diary (eDiary), capable of conducting home treatment and otherwise able to follow trial procedures

Exclusion criteria

For an eligible patient, all exclusion criteria had to be answered "no".

1. Known or suspected hypersensitivity to trial product including allergy to hamster protein or to related products
2. Previous participation in this trial defined as withdrawal after administration of trial product

3. Dosing of any investigational drug within 30 days prior to screening except for turoctocog alfa. (For Brazil only: Participation in other trials within one year prior to screening visit (visit 1) unless there is a direct benefit to the research subject at the Investigator's discretion)
4. Any history of FVIII inhibitors. For required documentation, see the protocol
5. FVIII inhibitors ≥0.6 BU, measured by Central Laboratory at screening
6. HIV positive, defined by medical records, with CD4+ count ≤200/µL or a viral load of >400000 copies/mL. If the data are not available in medical records within last 6 months, CD4+ will be measured at the screening visit
7. Congenital or acquired coagulation disorders other than haemophilia A
8. Previous significant thromboembolic event (e.g., myocardial infarction, cerebrovascular disease or deep vein thrombosis) as defined by medical records
9. Platelet count 3 times above the upper limit of normal reference ranges, measured by Central Laboratory at screening
10. ALT > 3 times above the upper limit of normal reference ranges, measured by Central Laboratory at screening
11. Creatinine level ≥1.5 times above the upper limit of normal reference ranges, measured by Central Laboratory at screening
12. Any disease (liver, kidney, inflammatory and mental disorders included) or condition which, according to the Investigator's judgement, could imply a potential hazard to the patient, interfere with trial participation or trial outcome
13. Surgery planned to occur during the main phase of the trial (exceptions are port placement, dental extractions, and minor, uncomplicated emergent procedures)
14. Ongoing treatment or planned treatment during the trial with chemotherapy, immunomodulatory agents (e.g., i.v. immunoglobulin, routine systemic corticosteroids)
15. Unwillingness, language or other barriers precluding adequate understanding and/or cooperation from parents or child
16. Documented diagnosis of obesity (only for patients in the PK part) defined as body mass index (BMI) equal to or greater than the 95th percentile for age for children ≥2 years

Trial ID: NN7088-4410

Inclusion criteria

According to the protocol, the inclusion criteria were as follows:

Patients are eligible to be included in the trial only if all of the following criteria apply:

1. Informed consent from the patient or the child's parent/LAR obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Male patients of all ages with the diagnosis of severe congenital haemophilia A (FVIII activity <1%) based on medical records
3. On-going participation in NN7088-3859 (pathfinder2), or NN7088-3885 (pathfinder5) at the time of transfer

4. The patient or child’s parent/LAR is willing to follow one of the defined turoctocog alfa pegol prophylaxis regimens
5. The patient and/or caregiver is capable of assessing a bleeding episode, capable of home treatment of bleeds and otherwise able to follow trial procedures

For an eligible patient, all inclusion criteria must be answered “yes”.

Exclusion criteria

According to the protocol, the exclusion criteria were as follows:

Patients are excluded from the trial if any of the following criteria apply:

1. Known or suspected hypersensitivity to trial product including allergy to hamster protein or related products
2. Any disorder, except for conditions associated with haemophilia, which in the investigator’s opinion might jeopardise patient’s safety or compliance with the protocol
3. Current participation in any clinical trial (except NN7088-3859 or NN7088-3885 (pathfinder2 or 5 respectively)) of an approved or non-approved investigational medicinal product
4. Mental incapacity, unwillingness to cooperate, or a language barriers precluding adequate understanding and cooperation

For an eligible patient, all exclusion criteria must be answered “no”.

Trial ID: NN7088-3908

Inclusion criteria:

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Male, age below 6 years of age at the time of signing informed consent
3. Diagnosis of severe haemophilia A (FVIII activity level 1%) based on medical records or central laboratory results
4. No prior use of purified clotting factor products (5 previous exposures to blood components is acceptable)

Exclusion criteria

1. Any history of FVIII inhibitor (defined by medical records) - Known or suspected hypersensitivity to trial product or related products
2. Previous participation in this trial. Participation is defined as first dose administered of trial product
3. Receipt of any investigational medicinal product within 30 days before screening
4. Congenital or acquired coagulation disorder other than haemophilia A
5. Any chronic disorder or severe disease which, in the opinion of the Investigator, might jeopardise the patient's safety or compliance with the protocol
6. Patient's parent(s')/legally acceptable representative (LAR(s')) mental incapacity, unwillingness to cooperate, or a language barrier precluding adequate understanding and cooperation

Treatments

Trial ID: NN7088-3885

Prophylaxis: 60 IU/kg (50–75 IU/kg) twice weekly

Surgery: An extra dose of N8-GP equivalent to the dose administered for a severe bleeding episode or aligned to local practice.

Treatment of bleeds: 20−75 IU/kg, according to the severity and location of the bleeding episode (recommended: Joint, muscle (except iliopsoas) 20–60 IU/kg, CNS/head, throat, neck, iliopsoas, gastrointestinal 40–75 IU/kg)

Trial ID: NN7088-4410

Prophylaxis: 60 IU/kg twice weekly

Surgery: An extra dose of N8-GP equivalent to the dose administered for a severe bleeding episode or aligned to local practice.

Treatment of bleeds: 20−75 IU/kg, according to the severity and location of the bleeding episode (mild: 20–60 IU/kg. Severe: 40–75 IU/kg)

Trial ID: NN7088-3908

Pre-prophylaxis (pt. less than 24 months of age): 60 IU/kg (50-75 IU/kg) on demand or slow start propohylaxis

Prophylaxis: 60 IU/kg (50–75 IU/kg) twice weekly

Surgery: An extra dose of N8-GP equivalent to the dose administered for a severe bleeding episode or aligned to local practice.

Treatment of bleeds: 20−75 IU/kg, according to the severity and location of the bleeding episode (mild: Joint, muscle (except iliopsoas) 20–60 IU/kg. Severe: CNS/head, throat, neck, iliopsoas, gastrointestinal 40–75 IU/kg)

Objectives

Primary objective

Table 5: Primary objectives

Trial ID	Primary Objectives
Previously treated patients	
3885	• To evaluate immunogenicity of N8-GP
4410	• To investigate the safety of turoctocog alfa pegol during continuous use for prevention and treatment of bleeding episodes of previously turoctocog alfa pegol treated severe haemophilia A patients.
Previously untreated patients	
3908	• To evaluate immunogenicity of N8-GP in previously untreated patients (PUPs) with severe haemophilia A.

Secondary objectives

Table 6: Secondary objectives

Trial ID	Efficacy related Objectives
Previously treated patients	
3885	• To evaluate the clinical efficacy of N8-GP in prophylaxis and treatment of bleeds • To evaluate the PROs
4410	• To investigate efficacy of N8-GP during prophylaxis treatment • To investigate haemostatic efficacy of N8-GP when used for treatment of bleeds • To investigate joint health status • To investigate haemostatic efficacy during major surgical interventions • To investigate treatment satisfaction in patients receiving N8-GP prophylaxis (PRO)
Previously untreated patients	
3908	• To evaluate the efficacy of N8-GP in PUPs during long-term prophylaxis treatment and for treatment of bleeding episodes.

Abbreviations: N8-GP = turoctocog alpha pegol; PK = pharmacokinetics; PROs = patient-reported outcomes; PUPs = previously untreated patients.

Outcomes/endpoints

Trial ID: NN7088-3885

Primary endpoint

- Incidence of inhibitory antibodies against FVIII ≥0.6 Bethesda units (BU) during the main phase of the trial (from 0-26 weeks of treatment)

Secondary endpoints

Safety endpoints

- Incidence of inhibitory antibodies against FVIII ≥0.6 BU during the extension phase of the trial (from 26 weeks to the last patient has completed the trial)
- Frequency of adverse events (AEs) including SAEs reported during the trial period

Efficacy endpoints

- Haemostatic effect of N8-GP when used for treatment of bleeding episodes and assessed as: Excellent, Good, Moderate, or None
- Number of bleeding episodes during prophylactic treatment with N8-GP (annualised bleeding rate)
- Consumption of N8-GP per bleeding episode (number of injections and U/kg
- Consumption of N8-GP during prophylaxis (number of injections and U/kg per month and year)
- Changes in PRO scores from baseline to the end of treatment in the main phase, and during the extension phase

Pharmacokinetics endpoints on previous FVIII product and N8-GP

- Incremental recovery (IR30min), (defined as the peak level recorded 30 min after end of injection and reported as [U/mL]/[U/kg])
- Area under the curve (AUC), (h×U/mL)
- Terminal half-life (t½), (h)
- Clearance (CL), (mL/h/kg)

Trial ID: NN7088-4410

Primary endpoint

- Number of adverse events reported

Secondary endpoints

- Incidence of FVIII inhibitors ≥0.6 BU
- Number of bleeding episodes on prophylaxis
- Number of spontaneous bleeding episodes on prophylaxis
- Haemostatic effect of N8-GP when used for treatment of bleeding episodes assessed as: Excellent, Good, Moderate, or None
- Number of N8-GP injections required per bleeding episode
- Pre-dose FVIII activity levels on N8-GP prophylaxis (IU/dL)
- Change in joint health status from start to end of trial (based on Haemophilia Joint Health Score)
- Haemostatic response during major surgical interventions assessed as: Excellent, Good, Moderate, or None
- Consumption of N8-GP (number of infusions and IU/kg) per bleed
- Consumption of N8-GP (number of infusions and IU/kg per month and per year) during prophylaxis treatment
- Change from start till end of trial in treatment satisfaction (based on Hemo-SAT score)

Exploratory endpoints

- Incidence of anti-N8-GP antibodies
- Incidence of anti-PEG antibodies

Trial ID: NN7088-3908

Primary Endpoint

- Incidence of FVIII inhibitors

Secondary Endpoint

- Frequency of Adverse events (AEs) including serious AEs and Medical Events of Special Interest (MESI)*
- Incidence of confirmed high titre inhibitors (defined as inhibitor titre > 5BU) *
- Number of breakthrough bleeding episodes during prophylaxis with N8-GP (annualised bleeding rate) *
- Haemostatic effect of N8-GP in treatment of bleeding episodes, assessed by a predefined 4- point haemostatic response scale (“excellent”, “good”, “moderate” and “none”) *
- Consumption of N8-GP for prophylaxis (number of injections and U/Kg per month and per year)
- Consumption of N8-GP for treatment of bleeding episodes (number of injections and U/Kg required per bleeding episode)

- Total consumption of N8-GP per patient (prevention and treatment of bleeding episodes) per month and annualised value

*Key supportive secondary endpoint prospectively selected for posting on clinicaltrials.gov

Sample size

Trial ID: NN7088-3885

No formal sample size calculations have been performed. The sample size is based on the EMA guideline from July 2011 requirement.

Trial ID: NN7088-4410

All patients participating in NN7088-3859 (pathfinder2) or NN7088-3885 (pathfinder5) fulfilling the inclusion and exclusion criteria of this trial were eligible to participate where continuous safety assessments were made.

Trial ID: NN7088-3908

No formal sample size calculations have been performed. The sample size of 100 completers is based on EMA guideline.

Randomisation

No randomisation was performed due to the open-label nature of the trials with no comparator.

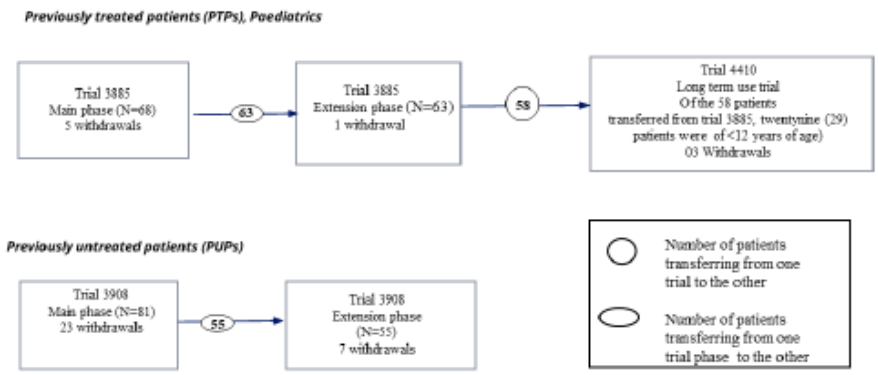
Blinding (masking)

All trials (3885, 4410, and 3908) were open-labelled. There was no randomisation in trials due to the single-arm design of the trials.

Results

Participant flow

Figure 12: Patients (<12 years of age) flow in trials collecting efficacy in the N8-GP clinical development programme



Note: Prior to entering the extension phase(s) of the trials, patients had to re-consent to continue.
Abbreviations: N=Number of exposed patients.

Table 7: Patient disposition in trial 3885

	Younger children (0 - 5 years)	Older children (6 - 11 years)	Total
Screened	37	35	72
Exposed, N(%)	34(100.0)	34(100.0)	68(100.0)
Full analysis set, N(%)	34(100.0)	34(100.0)	68(100.0)
Safety analysis set, N(%)	34(100.0)	34(100.0)	68(100.0)
Withdrawal in main phase, N(%)	5(14.7)	0(0.0)	5(7.4)
AE	2(5.9)	0(0.0)	2(2.9)
Other	2(5.9)	0(0.0)	2(2.9)
Withdrawal criteria	1(2.9)	0(0.0)	1(1.5)
Completed main phase, N(%)	29(85.3)	34(100.0)	63(92.6)
Continued into extension phase, N(%)	29(85.3)	34(100.0)	63(92.6)
Withdrawal in extension phase, N(%)	1(2.9)	0(0.0)	1(1.5)
Other	1(2.9)	0(0.0)	1(1.5)
Completed extension phase, N(%)*	28(96.6)	34(100.0)	62(98.4)
Withdrawal in entire study, N(%)**	6(17.6)	0(0.0)	6(8.8)
Completed entire study, N(%)**	28(82.4)	34(100.0)	62(91.2)
Undergone minor surgery, N(%)***	9(26.5)	14(41.2)	23(33.8)
Years in trial	139	167	306
EDs in trial	14596	17542	32138

* Calculated as a percentage of those entering extension phase.
** Calculated as a percentage of those exposed to treatment.
*** Minor surgery during trial
The full analysis set and the safety analysis set both consist of all patients exposed to N8-GP
ED: Exposure days
nn7088-3885/ctr_i3_20190218_er - 18-FEB-2019 - t_1420_patdisp/14200010_pt_disp.txt

Table 8: Patient disposition trial 4410

	Once weekly	Twice weekly	Three times weekly	Total
Screened				160
Coming from 3859	25	76	1	102
Coming from 3885	0	57	1	58
Treatment at start of trial for exposed patients	25	133	2	160
Patients switching from once weekly to	-	2	0	2
Patients switching from twice weekly to	-	-	5	5
Patients switching from three times weekly to	-	0	-	0
Exposed	25	135	7	160
Full analysis set	25	135	7	160
Safety analysis set	25	135	7	160
Completed trial, N(%)	23 (92.0)	114 (84.4)	7 (100.0)	144 (90.0)
Withdrawal during trial, N(%)	0 (0.0)	16 (11.9)	0 (0.0)	16 (10.0)
Lost to follow-up, N(%)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.6)
Protocol deviation, N(%)	0 (0.0)	3 (2.2)	0 (0.0)	3 (1.9)
Withdrawal by subject, N(%)	0 (0.0)	7 (5.2)	0 (0.0)	7 (4.4)
Withdrawal by parent/guardian, N(%)	0 (0.0)	5 (3.7)	0 (0.0)	5 (3.1)
Undergone minor surgery, N(%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Undergone major surgery, N(%)	3 (12.0)	9 (6.7)	0 (0.0)	12 (7.5)
Years in trial*	46.2	241.4	8.3	298.2
EDs in trial	2556	24922	1217	28698

Patients may be summarised under more than one treatment if they switched regimen during the study. However events will only be represented under the treatment where they happened.
* Years in trial is from screening visit until date of last contact.
ED: exposure days.

Table 9: Patient disposition in trial 3908:

	Pre-prophylaxis	Prophylaxis	ITI	Total
Screened				88
Screening failures				6
Enrolled				82
Exposed to N8-GP				81
Treatment regimen at first exposure to N8-GP	55	26	-	81
Patients switching from pre-prophylaxis		42	2	44
Exposed, N (%)	55 (100.0)	69* (100.0)	8 (100.0)	81 (100.0)
Full analysis set, N (%)	55 (100.0)	69 (100.0)	8 (100.0)	81 (100.0)
Safety analysis set, N (%)	55 (100.0)	69 (100.0)	8 (100.0)	81 (100.0)
Completed main phase, N (%)	- (0.0)	55 (79.7)	- (0.0)	55 (67.9)
Withdrawal during main phase, N (%)	11 (20.0)	10 (14.5)	2 (25.0)	23 (28.4)
Adverse events	3 (5.5)	4 (5.8)	0 (0.0)	7 (8.6)
Lack of efficacy	1 (1.8)	1 (1.4)	1 (12.5)	3 (3.7)
Lost to follow-up	0 (0.0)	1 (1.4)	0 (0.0)	1 (1.2)
Protocol violation	1 (1.8)	1 (1.4)	0 (0.0)	2 (2.5)
Withdrawal by parent/guardian	1 (1.8)	2 (2.9)	1 (12.5)	4 (4.9)
Withdrawal by subject	2 (3.6)	0 (0.0)	0 (0.0)	2 (2.5)
Other	3 (5.5)	1 (1.4)	0 (0.0)	4 (4.9)
Entered extension phase, N (%)	0 (0.0)	55 (79.7)	0 (0.0)	55 (67.9)
Withdrawal during extension, N (%)	0 (0.0)	7 (10.1)	0 (0.0)	7 (8.6)
Adverse events	0 (0.0)	1 (1.4)	0 (0.0)	1 (1.2)
Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	0 (0.0)	1 (1.4)	0 (0.0)	1 (1.2)
Withdrawal by parent/guardian	0 (0.0)	1 (1.4)	0 (0.0)	1 (1.2)
Withdrawal by subject	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	4 (5.8)	0 (0.0)	4 (4.9)
Completed extension phase, N (%)	0 (0.0)	49 (71.0)	0 (0.0)	49 (60.5)
Completed the full trial*, N (%)	27 (49.1)	49 (71.0)	4 (50.0)	49 (60.5)
Undergone minor surgery, N (%)	10 (18.2)	16 (23.2)	2 (25.0)	27 (33.3)
Undergone major surgery, N (%)	0 (0.0)	3 (4.3)	0 (0.0)	3 (3.7)
Years in trial+	27.1	197.2	9.5	233.8
Exposure days in trial	428	16242	1514	18184
Main phase	428	2882	1396	4706
Extension phase	-	13360	118	13478

Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns, with data from the relevant period.
+ Years in trial: Sum of years in trial for all patients (for discontinued patients time from discontinuation of treatment to end of trial is excluded).
The full analysis set and the safety analysis set both consists of all patients exposed to N8-GP.
A screening period is allowed in this trial. This can cause a difference in the count of screened vs. exposed patients. One patient switched to prophylaxis from ITI.
*Four patients considered as completers due to early study closure at 3 sites (2 Main + 2 Extension)
**One patient switched from Pre-prophylaxis to ITI and then to prophylaxis on completion of ITI.

Recruitment

Trial ID: NN7088-3885

The trial was conducted at 77 sites in 22 countries, as follows: Australia: 3 sites; Brazil: 1 site; Croatia: 1 site; Denmark: 2 sites; France: 3 sites; Germany: 5 sites; Hungary: 2 sites; Israel: 1 site; Italy: 2 sites; Japan: 8 sites; Malaysia: 2 sites; Netherlands: 2 sites; Norway: 1 site; Russia: 1 site; South Korea: 1 site; Spain: 2 sites; Sweden: 1 site; Switzerland: 3 sites; Taiwan: 2 sites; Turkey: 3 sites; United Kingdom; 6 sites; United States: 25 sites

Initiation date: 30.01.2012

Completion date main phase: 28.01.2014

Completion date extension phase: 10.12.2018

Trial ID: NN7088-4410

58 patients who completed trial 3885 moved on to trial 4410, 29 of which were <12 years old at the time.

The trial was conducted at 66 sites in 25 countries, as follows: Australia : 2 sites; Brazil : 1 site; Canada : 1 site; Croatia : 1 site; Denmark : 1 site; France : 2 sites; Germany : 2 sites; Greece : 1 site; Hungary : 2 sites; Israel : 1 site; Italy : 2 sites; Japan : 3 sites; Korea, Republic of : 1 site; Lithuania : 1 site; Malaysia : 1 site; Netherlands : 2 sites; Norway : 1 site; Portugal : 1 site; Spain : 2 sites; Switzerland : 4 sites; Taiwan : 1 site; Turkey : 5 sites; Ukraine : 1 site; United Kingdom : 8 sites; United States : 19 sites

Initiation date: 30.04.2018

Completion date: 03.12.2020

Trial ID: NN7088-3908

The trial was conducted in 31 trial sites sited in 14 countries: Australia : 2 sites; Austria : 2 site; Bulgaria : 1 site; Canada : 1 site; Germany : 1 site; Greece : 2 sites; Israel : 1 sites; Italy : 1 site; Japan : 3 sites; Malaysia : 3 site; Spain : 2 sites; Taiwan : 1 site; Thailand : 3 sites; United States : 8 sites.

Initiation date: 26.06.2014

Completion date: 11.11.2021

Conduct of the study

Trial ID: NN7088-3885

Protocol amendments

There were 5 global amendments to the protocol; see *Table* **10:**. None of the amendments issued after first patient first visit were considered to have any influence on the interpretation of the results of the trial. All protocol amendments were approved according to local requirements prior to implementation.

Table 10: 3885 - Protocol amendments

Amendment number	Issue date	Timing of change (before/after FPFV)	Countries affected	Key changes
1	02-Nov-2012	Before	Global	• Changes introduced to the dose table in order to extend weight predictions. • Port restrictions text in connection with blood samplings removed. Included together with detailed instructions for laboratory sampling in other trial documents (e.g., in the laboratory manual). • Inconsistencies and typing errors corrected
2	03-Feb-2014	After	Global	• Withdrawal criteria amended to allow patients with a low titre inhibitor (≤5 BU), that does not result in

Amendment number	Issue date	Timing of change (before/after FPFV)	Countries affected	Key changes
				clinically ineffective treatment with N8-GP, to continue in the trial[a]. • Reference unit for inhibitors has been aligned to BU. • Lupus anticoagulant added to flowchart main and extension phase. • Patients allowed continuing in the extension phase as soon as minimum 25 patients for each cohort had completed the main phase. • List of participating countries updated. • FVIII results to investigators changed to one-stage clotting assay to align across N8-GP project. • Inclusion of an assay to analyse for antibodies towards PEG. • Clarification that FVIII activity should be analysed in case of severe allergic reaction. • Labelling allowed by third party vendors. • Section added: suspected transmission of infectious agents to the SAE definition. • Extension of monitoring window during extension phase to reflect the visit scheduled. • Multiple bleeding from the same event or time point counted as one bleeding episode. • Minor updates to the interim analysis
3	07-Apr-2014	After	Global	• Patients with low titre inhibitors who continue on N8-GP treatment are followed systematically and should attend an unscheduled visit monthly [b]. • Novo Nordisk safety committee consulted by the investigator to determine the best management of individual patients with low titre inhibitors [b].
4	28-Apr-2016	After	Global	• Monitoring of antibody development against HCP antibodies has been included under laboratory assessments based on a recommendation from FDA.
5	15-Dec-2016	After	Global	• Prolonged storage of leftover blood samples to enable further characterisation as new biomarkers related to the disease or related diseases and/or safety, efficacy or mechanism of action may evolve.

Abbreviations: BU, Bethesda Unit; FDA, United States Food and Drug Administration; FPFV, first patient first visit; FVIII, coagulation factor VIII; HCP, host cell protein; N8-GP, glycoPEGylated turoctocog alfa; PEG, polyethylene glycol; SAE, serious adverse event

[a]To meet current treatment practices in haemophilia A where patients with low titre inhibitors continue treatment with FVIII until the inhibitor interferes with prophylaxis or treatment of bleeds at standard doses of FVIII. 23 In addition, some low titre inhibitors may be transient, disappearing within 6 months of initial documentation, despite recent antigenic challenge with factor concentrate.

[b]This amendment was implemented following a request from the VHP (Participating Member States: France, Portugal and United Kingdom) involved in trial 3885.

Changes to the planned statistical analysis

Initially, it was planned to report the extension phase analysis separately when the trial had been completed. However, it was decided to perform an interim analysis during the extension phase of the trial while it was ongoing for the marketing authorisation application. All endpoints in the current CTR were based on accumulated data from the main and extension phase. To evaluate the safety and efficacy of N8-GP from the pivotal production process and the commercial production process, a subgroup analysis was conducted including only those patients exposed to N8-GP from both processes. The results from this subgroup analysis are reported in the interim extension phase CTR.

Pharmacokinetics endpoint estimation

Half-life values were estimated using the population-based method that allowed inclusion of all data (including data below lower limit of quantification (LLOQ)). The t½ for the previous FVIII product was estimated using time points from 1 to 30 hours, while for N8-GP, t½ was estimated using time points from 6 to 96 hours. The planned analysis where individual t½ was to be derived based on the patient's data alone was not used. This is because patients with higher clearance were more likely to have measurements below LLOQ at the later measurement time points and λz was not estimated for these patients when there were two or less remaining data points above LLOQ. Thus, the mean half-life would have been upward biased using the planned analysis. Based on the updated half-life estimate, all PK parameters dependent on this estimate have been recalculated for this current CTR.

Main analytical assay

As for the analysis of combined main and extension phase, additional analysis based on the chromogenic assay using PSS as calibrator has been included.

Trial ID: NN7088-4410

Changes in trial conduct

There were 2 amendments to the protocol.

Table 11: 4410 - Protocol amendments

Amendment number	Issue date	Timing of change (before/after FPFV)	Countries affected	Key changes
1	10 August 2018	After	France	Update to Section 8.1 Discontinuation of trial product: Criteria 9 was added "In the case of a major thromboembolic event (e.g. myocardial infarction, cerebrovascular disease or deep venous thrombosis) as per investigator"

Amendment number	Issue date	Timing of change (before/after FPFV)	Countries affected	Key changes
2	18 June 2019	After	Global (The amendment was rejected in Norway)	Visits 2, 4, 6 and 8 could be conducted as phone visits for patients receiving trial drug at home as part of the 'Direct to Patient' (DTP) programme. The choice of vial strength for each patient was based on the body weight at the last scheduled visit conducted in trial NN7088-3859 or 3885 prior to the initial shipment of trial product in current trial NN7088-4410. This was to ensure availability of trial product at the start of trial. Added that patients may be discontinued from the trial when commercial N8-GP becomes available in their respective country. Trial discontinuation will allow for patients to undertake commercial treatment instead of participating in a clinical trial. Sentence in the haematology section deleted to clarify that only FVIII activity must be taken 30 min post dose, not haematology. "Web-portal for document exchange" section added to appendix 3 – Trial governance considerations. A few minor administrative changes performed.

Changes due to COVID-19 pandemic

Trial sites temporarily closed for patient visit due to COVID-19 pandemic Twenty (20) out of 66 trial sites were temporarily closed for patient's visit due to COVID-19 pandemic during the trial. Many patients were also unable to attend their respective sites due to travel restrictions. Due to these issues the patient visits at these affected sites were converted to a phone visit to collect the data as applicable verbally to secure patient's safety.

Table 12: 4410 - Trial sites affected by COVID-19 pandemic

Country	Number of sites affected
Canada	1
France	1
United Kingdom	7
United States	10
Netherlands	1

Changes to site monitoring

Due to COVID-19 pandemic restrictions, many site monitors could not travel to the sites to perform on site monitoring visits as planned in the protocol. These onsite monitoring visits were converted to off-site monitoring visits. In total, 77 on-site monitoring visits at 36 sites were converted to off-site monitoring visits.

Changes to source data verification (SDV)

The SDV was carried out as planned at majority of the trial sites except for sites in 5 countries (Canada, US, Italy, UK and Malaysia). An internal risk assessment was done for these sites in case of remote SDV or no SDV. In case of remote SDV the data checks related to primary and secondary endpoints were prioritised followed by other checks in the monitoring plan. An internal risk assessment team also assessed and confirmed the missing SDV during the trial as low risk.

In total, 38 patients (at 17 sites) required remote SDV after EoT visit due to COVID-19 pandemic restrictions:

- Of these 38 patients, SDV was performed completely for 25 patients at 12 sites (in the manner that was expected during on-site monitoring visit).
- For 10 patients at 4 sites, the remote SDV could not be performed due to various reasons including remote SDV being prohibited by local legislation. The 5 affected sites were in Malaysia, US and Italy. Some of these sites also had a monitoring back-log from earlier on in the pandemic and therefore, for several visits (visit 8 and EoT visit in all cases, and visits 6 and 7 in some cases) SDV was not performed in time for DBL.
- For 3 patients (at 1 site in US) the SDV was missing for diary and lab data.

Drug accountability reconciliation

Due to COVID-19 pandemic restrictions, drug accountability reconciliation was performed remotely for 17 patients at 9 sites (1 site in Italy, 1 site in Malaysia and 7 sites in US). At one of the 7 sites in the US, the remote drug accountability reconciliation was performed after the local site had performed the IMP destruction (due to local law) affecting 3 patients.

Trial ID: NN7088-3908

There were 8 amendments to the protocol. With protocol amendment no. 8 (15-Jun-2020), recruitment to the trial was terminated, which meant that less than 100 patients, as originally planned, completed the trial.

Table 13: 3908 - protocol amendments

Amendment number	Issue date	Timing of change	Countries affected	Key changes
1	Not finalised	NA	Portugal	The protocol amendment was dedicated to Portugal but was never finalised. Due to SOP requirements the countries were required to have their own logs which would only cover global amendments

Amendment number	Issue date	Timing of change	Countries affected	Key changes
2	20 March 2015	After FPFV	Global	Detailed information on major surgery and ITI, extended trial timelines
3	01 November 2016	After FPFV	Global	This protocol amendment included a new secondary endpoint to assess the ITI treatment outcome and included monitoring of antibody development against Host Cell Protein (HCP).
4	14 June 2018	After FPFV	Israel	This protocol amendment was for Israel seeking permission to obtain the F8 genotype.
5	13 June 2019	After FPFV	Global	This protocol amendment specified interim analysis when approximately 45 patients had reached 50 EDs each, and additional administrative changes
6	21 June 2019	After FPFV	Israel	This protocol amendment for Israel was to obtain informed consent from withdrawn patients to provide genotype results
7	02 July 2019	After FPFV	Japan	This protocol amendment for Japan was due to that the regulatory category of this clinical trial should be updated in accordance with Japanese regulations. This was mandatory before NNPL could obtain marketing approval of N8-GP
8	15 June 2020	After FPFV	Global	This protocol amendment specified the closure of recruitment to the trial, and that more than 50 but less than 100 patients would complete the trial. LPLV date 13 November 2021 was kept. Due to the observations of non-inhibitor patients with low IR, anti-PEG IgG and additional IgM antibody analyses were added to the assessments.

Baseline data

Trial ID: NN7088-3885

Overall, 68 patients were dosed with N8-GP in trial 3885, of which 34 patients were 0−5 years of age and 34 patients were 6−11 years of age. A total of 63 patients completed the main phase of the trial and continued into the extension phase and 62 patients completed the extension phase of the trial.

Patients were recruited from 36 sites in 15 countries worldwide. The trial population consisted of male patients, the majority of whom were 'White' (81%). The remainder of patients were 'Asian' (7%), 'Black or African American' (4%), 'Other' (3.0%) or not reported (4%).

At baseline, the patients in the 0–5 years age-group were characterised by a mean (range) age: 3.0 (0–5) years and mean (SD) BMI: 16.3 (1.9). Patients in the 6–11 years age-group were of mean (range) age: 8.9 (6-11) years and mean (SD) BMI: 17.9 (3.4).

All patients were previously treated with no history of inhibitors. The mean (SD) number of EDs to other FVIII products before trial entry were: 206.9 days (153.4) EDs for the 0-5 years age-group and 809.9 days (400.6) for the 6–11 years age-group. The majority (65/68 patients) were on prophylaxis with other FVIII products and the remainder of the patients received on-demand treatment (3/68 patients) prior to enrolment in the trial.

In total, 13 out of 68 patients (19%) had target joints at baseline: 5 patients in the 0-5 years age-group and 8 patients in the 6-11 years age-group. A total of 6 (9%) patients (3 in each age-group) had clinically significant abnormal findings in the musculoskeletal system at baseline related to haemophilia A.

Table 14: Baseline demographics - full analysis set

	Younger children (0 - 5 years)	Older children (6 - 11 years)	Total
Number of patients	34	34	68
Age at baseline (years)			
N	34	34	68
Mean (SD)	3.0 (1.3)	8.9 (1.7)	6.0 (3.3)
Median	3.0	9.0	5.5
Min ; Max	1 ; 5	6 ; 11	1 ; 11
Country, N (%)			
N	34 (100.0)	34 (100.0)	68 (100.0)
Canada	-	2 (5.9)	2 (2.9)
France	4 (11.8)	3 (8.8)	7 (10.3)
Germany	1 (2.9)	-	1 (1.5)
Greece	-	1 (2.9)	1 (1.5)
Israel	-	2 (5.9)	2 (2.9)
Italy	-	1 (2.9)	1 (1.5)
Japan	-	2 (5.9)	2 (2.9)
Lithuania	1 (2.9)	4 (11.8)	5 (7.4)
Malaysia	1 (2.9)	1 (2.9)	2 (2.9)
Portugal	-	2 (5.9)	2 (2.9)
Switzerland	2 (5.9)	2 (5.9)	4 (5.9)
Turkey	2 (5.9)	4 (11.8)	6 (8.8)
Ukraine	6 (17.6)	-	6 (8.8)
United Kingdom	5 (14.7)	1 (2.9)	6 (8.8)
United States of America	12 (35.3)	9 (26.5)	21 (30.9)
Ethnicity, N (%)			
N	34 (100.0)	34 (100.0)	68 (100.0)
Hispanic or Latino	-	3 (8.8)	3 (4.4)
Not Hispanic or Latino	34 (100.0)	30 (88.2)	64 (94.1)
NA	-	1 (2.9)	1 (1.5)
Race, N (%)			
N	34 (100.0)	34 (100.0)	68 (100.0)
White	30 (88.2)	25 (73.5)	55 (80.9)
Black or African American	2 (5.9)	1 (2.9)	3 (4.4)
Asian	1 (2.9)	4 (11.8)	5 (7.4)
Other	1 (2.9)	1 (2.9)	2 (2.9)
NA	-	3 (8.8)	3 (4.4)

NA: not applicable

Table 15: Body measurements at baseline - full analysis set

	Younger children (0 - 5 years)	Older children (6 - 11 years)	Total
Number of patients	34	34	68
Height (cm)			
N	34	34	68
Mean (SD)	99.3 (10.8)	136.0 (13.9)	117.6 (22.3)
Median	100.9	136.0	116.8
Min ; Max	80.0 ; 120.0	111.1 ; 160.5	80.0 ; 160.5
Body weight (kg)			
N	34	34	68
Mean (SD)	16.1 (3.4)	34.1 (11.5)	25.1 (12.4)
Median	16.1	33.8	20.6
Min ; Max	10.9 ; 23.0	17.0 ; 60.4	10.9 ; 60.4

The baseline value for height is the measurement at screening visit 1
The baseline value for weight is the value from visit 2
If the visit 2 value for weight was missing, the value from visit 1 was used as baseline

Haemophilia and treatment history

The patient's full haemophilia and inhibitor history is outlined in *Table*. All patients included in the trial were males with severe congenital haemophilia A (FVIII activity <1%) according to medical records with no history of inhibitors (thereby fulfilling the specified inclusion criteria).

A total of 30 patients (44.1%) reported history of haemophilia A among relatives.

Mean (range) number of Eds to other FVIII products before trial entry were 207 (51-567) Eds for the 0-5 year age group and 810 (164-1627) Eds for the 6-11 year age group.

Prior to enrolment in the trial, 65 (96%) of the patients were on prophylactic treatment (61 on rFVIII and 4 on plasma-derived FVIII products). The remaining 3 (4%) patients were on on-demand treatment. For patients previously on prophylactic treatment (n=65), mean dose of the previous FVIII product was 33.7 IU/kg and median ABR was 4.0. Previously on-demand patients (n=3) reported a mean dose of 23.3 IU/kg and a median ABR of 12.

Table 16: Trial 3885 Haemophilia and inhibitor history

	Younger children (0 - 5 years)	Older children (6 - 11 years)	Total
Number of patients	34	34	68
Classification of haemophilia A*, N (%)			
N	34 (100.0)	34 (100.0)	68 (100.0)
Severe	34 (100.0)	34 (100.0)	68 (100.0)
History of haemophilia A among relatives, N (%)			
N	34 (100.0)	34 (100.0)	68 (100.0)
Yes	17 (50.0)	13 (38.2)	30 (44.1)
No	17 (50.0)	19 (55.9)	36 (52.9)
Unknown	-	2 (5.9)	2 (2.9)
Relatives with haemophilia A and inhibitors**, N (%)			
N	17 (100.0)	13 (100.0)	30 (100.0)
Siblings / cousins	1 (5.9)	3 (23.1)	4 (13.3)
Siblings / cousins, maternal uncle	-	2 (15.4)	2 (6.7)
Siblings / cousins, maternal grandfather	1 (5.9)	4 (30.8)	5 (16.7)
Siblings / cousins, maternal uncle, maternal grandfather	1 (5.9)	-	1 (3.3)
Maternal uncle	6 (35.3)	2 (15.4)	8 (26.7)
Maternal grandfather	3 (17.6)	1 (7.7)	4 (13.3)
None	5 (29.4)	1 (7.7)	6 (20.0)
Total number of exposure days prior to trial entry			
N	34	34	68
Mean (SD)	206.9 (153.4)	809.9 (400.6)	508.4 (427.6)
Median	160.0	790.0	367.0
Min ; Max	51.0 ; 567	164 ; 1627	51.0 ; 1627
Clinical suspicion of inhibitors, N (%)			
N	34 (100.0)	34 (100.0)	68 (100.0)
Yes	1 (2.9)	1 (2.9)	2 (2.9)
No	33 (97.1)	33 (97.1)	66 (97.1)
Result of FVIII inhibitor tests, N (%)			
N	34 (100.0)	34 (100.0)	68 (100.0)
Negative	34 (100.0)	34 (100.0)	68 (100.0)
Has the patient switched FVIII product since diagnosis with Haemophilia A, N (%)			
N	34 (100.0)	34 (100.0)	68 (100.0)
Yes	17 (50.0)	24 (70.6)	41 (60.3)
No	17 (50.0)	10 (29.4)	27 (39.7)
Type of FVIII product, N (%)			
N	34 (100.0)	34 (100.0)	68 (100.0)
Plasma FVIII product	-	4 (11.8)	4 (5.9)
Recombinant FVIII	34 (100.0)	30 (88.2)	64 (94.1)

*If classified as mild or moderate, inclusion criteria 2 is violated.
** N in this block refers to the number of patients who answered 'yes' to the question 'History of relatives with haemophilia'.

Table 17: Trial 3885 treatment history - full analysis set

	Younger children (0 - 5 years)	Older children (6 - 11 years)	Total
Number of patients	34	34	68
Current treatment prior to trial, N (%)			
N	34 (100.0)	34 (100.0)	68 (100.0)
Prophylaxis regimen	31 (91.2)	34 (100.0)	65 (95.6)
On-demand	3 (8.8)	-	3 (4.4)
Previous prophylaxis patients:			
FVIII product given, N (%)			
N	31 (100.0)	34 (100.0)	65 (100.0)
Recombinant FVIII	31 (100.0)	30 (88.2)	61 (93.8)
Plasma FVIII product	-	4 (11.8)	4 (6.2)
Dose level (IU/kg)*			
N	29	34	63
Mean (SD)	35.5 (10.4)	32.1 (12.5)	33.7 (11.6)
Median	35.0	26.0	30.0
Min ; Max	20 ; 52	10 ; 60	10 ; 60
Common doses used to treat a bleed			
N	29	34	63
Mean (SD)	1.7 (1.1)	1.7 (0.8)	1.7 (1.0)
Median	1.0	2.0	1.0
Min ; Max	1 ; 6	1 ; 4	1 ; 6
Annual Bleeding rate			
N	31	34	65
Mean (SD)	4.6 (4.0)	7.9 (8.6)	6.4 (7.0)
Median	3.0	5.0	4.0
Min ; Max	0 ; 17	0 ; 36	0 ; 36
Number of bleeding episodes within the last 12 months**			
N	31	34	65
Mean (SD)	2.6 (2.9)	6.0 (6.6)	4.4 (5.4)
Median	2.0	4.0	3.0
Min ; Max	0 ; 13	0 ; 24	0 ; 24
Previous on-demand patients:			
FVIII product given, N (%)			
N	3 (100.0)	-	3 (100.0)
Recombinant FVIII	3 (100.0)	-	3 (100.0)
Dose level (IU/kg)			
N	3	0	3
Mean (SD)	23.3 (2.9)	- (-)	23.3 (2.9)
Median	25.0	-	25.0
Min ; Max	20 ; 25	- ; -	20 ; 25
Common doses used to treat a bleed			
N	3	0	3
Mean (SD)	1.7 (0.6)	- (-)	1.7 (0.6)
Median	2.0	-	2.0
Min ; Max	1 ; 2	- ; -	1 ; 2
Annual Bleeding rate			
N	3	0	3
Mean (SD)	16.3 (11.2)	- (-)	16.3 (11.2)
Median	12.0	-	12.0
Min ; Max	8 ; 29	- ; -	8 ; 29
Number of bleeding episodes within the last 12 months			
N	3	0	3
Mean (SD)	22.7 (19.3)	- (-)	22.7 (19.3)
Median	12.0	-	12.0
Min ; Max	11 ; 45	- ; -	11 ; 45

* Two patients reported the dose level in U instead of IU/kg and therefore the values are excluded.
** If less than 12 months on prophylaxis only the number of bleeding episodes during the period on prophylactic treatment should be recorded.

Table 18: Trial 3885 joint status at baseline - full analysis set

	Younger children (0 - 5 years)	Older children (6 - 11 years)	Total
Number of patients	34	34	68
Target joints			
Number of patients with target joints, N (%)	6 (17.6)	9 (26.5)	15 (22.1)
Joint location, N (%)			
N	8 (100.0)	11 (100.0)	19 (100.0)
Left ankle	2 (25.0)	2 (18.2)	4 (21.1)
Left knee	2 (25.0)	1 (9.1)	3 (15.8)
Left toe(s)	-	1 (9.1)	1 (5.3)
Right ankle	1 (12.5)	3 (27.3)	4 (21.1)
Right elbow	1 (12.5)	1 (9.1)	2 (10.5)
Right finger(s)	-	1 (9.1)	1 (5.3)
Right knee	2 (25.0)	1 (9.1)	3 (15.8)
Right toe(s)	-	1 (9.1)	1 (5.3)
Bleeds in target joints per patient			
N	5	9	14
Mean (SD)	6.0 (2.4)	4.4 (2.9)	5.0 (2.7)
Median	6.0	4.0	4.5
Min ; Max	4 ; 10	0 ; 9	0 ; 10
Bleeds in target joints per location			
N	7	11	18
Mean (SD)	4.3 (1.3)	3.6 (2.0)	3.9 (1.7)
Median	4.0	3.0	4.0
Min ; Max	3 ; 6	0 ; 8	0 ; 8
Joints with arthropathy			
Number of patients with arthropathy	4	1	5
Joint location, N (%)			
N	5 (100.0)	2 (100.0)	7 (100.0)
Left ankle	1 (20.0)	1 (50.0)	2 (28.6)
Left knee	1 (20.0)	-	1 (14.3)
Right ankle	-	1 (50.0)	1 (14.3)
Right elbow	1 (20.0)	-	1 (14.3)
Right knee	2 (40.0)	-	2 (28.6)
Degree of arthropathy, N (%)			
N	5 (100.0)	2 (100.0)	7 (100.0)
Mild	3 (60.0)	2 (100.0)	5 (71.4)
Moderate	2 (40.0)	-	2 (28.6)

A target joint is defined as three or more bleeds in a period of 6 months in a particular joint.
A problem joint is a joint which during the patient's life has caused special problems, in terms of repeated or frequent bleeding episodes.

Vital signs at baseline

Measurements of vital signs (systolic/diastolic blood pressure, pulse and body temperature) were not performed at baseline.

Trial ID: NN7088-4410

A total of 160 patients were enrolled and exposed to N8-GP in Trial 4410. Of these 160 patients, 102 patients were adolescent or adults from Trial 3859 and 58 patients (of which 29 patients were children aged <12 years and 29 were adolescent aged ≥12 years at the baseline during Trial 4410) from Trial 3885. All the 29 children were started on twice-weekly regimen with N8-GP, of which one patient switched to three-times weekly regimen with N8-GP post 139 Eds. A total of 3 children withdrew during the trial, none of the children withdrew due to an AE.

Overall, the entire trial population consisted of male patients with severe haemophilia A. Of the 29 children majority were 'White'(N=25) followed by 'Black or African American' (N=2), 'Asian' (N=1) and 'not reported' (N=1).

All patients were previously treated with N8-GP and had no history of inhibitors. Thirteen (13) patients used plasma derived FVIII products and 121 used recombinant products. Prior to enrolment in the previous trials (3859 and 3885), the majority (134/160 patients) were on prophylaxis treatment. The remainder of the patients received on-demand treatment (26/160 patients).

Overall, across age-group, total of 22 (13.8%) patients had clinically significant abnormal findings in the musculoskeletal system at baseline, probably as a result of their haemophilia A. The majority of these (14 patients) were on twice-weekly dosing regimen. A total of 5 patients had 7 target joints at baseline.

Table 19: Trial 4410 baseline body measurements at baseline

	Once weekly	Twice weekly	Three times weekly	Total
Number of patients	25	135	7	160
Age (years)				
N	25	135	7	160
Mean (SD)	35.1 (12.7)	27.3 (16.8)	25.3 (17.8)	28.4 (16.4)
Median	30.0	27.0	16.0	28.5
Min ; Max	21 ; 64	5 ; 72	7 ; 58	5 ; 72
Age groups, N (%)				
N	25 (100.0)	135 (100.0)	7 (100.0)	160 (100.0)
0-11 years	-	29 (21.5)	1 (14.3)	29 (18.1)
12-17 years	-	28 (20.7)	3 (42.9)	29 (18.1)
>=18 years	25 (100.0)	78 (57.8)	3 (42.9)	102 (63.8)
Country, N (%)				
N	25 (100.0)	135 (100.0)	7 (100.0)	160 (100.0)
Australia	1 (4.0)	1 (0.7)	-	2 (1.3)
Brazil	-	2 (1.5)	-	2 (1.3)
Canada	-	2 (1.5)	1 (14.3)	2 (1.3)
Croatia	-	3 (2.2)	-	3 (1.9)
Denmark	1 (4.0)	4 (3.0)	-	5 (3.1)
France	1 (4.0)	6 (4.4)	-	7 (4.4)
Germany	1 (4.0)	3 (2.2)	-	4 (2.5)
Greece	-	1 (0.7)	-	1 (0.6)
Hungary	-	9 (6.7)	1 (14.3)	9 (5.6)
Israel	3 (12.0)	3 (2.2)	-	6 (3.8)
Italy	3 (12.0)	4 (3.0)	-	6 (3.8)
Japan	1 (4.0)	5 (3.7)	-	6 (3.8)
Lithuania	-	4 (3.0)	-	4 (2.5)
Malaysia	2 (8.0)	2 (1.5)	1 (14.3)	5 (3.1)
Netherlands	-	4 (3.0)	-	4 (2.5)
Norway	-	1 (0.7)	-	1 (0.6)
Portugal	-	2 (1.5)	-	2 (1.3)
South Korea	-	4 (3.0)	-	4 (2.5)
Spain	-	2 (1.5)	-	2 (1.3)
Switzerland	1 (4.0)	7 (5.2)	2 (28.6)	8 (5.0)
Taiwan, Province of China	-	3 (2.2)	-	3 (1.9)
Turkey	5 (20.0)	9 (6.7)	1 (14.3)	13 (8.1)
Ukraine	-	5 (3.7)	-	5 (3.1)
United Kingdom	4 (16.0)	12 (8.9)	-	16 (10.0)
United States	2 (8.0)	37 (27.4)	1 (14.3)	40 (25.0)
Ethnicity, N (%)				
N	25 (100.0)	135 (100.0)	7 (100.0)	160 (100.0)
Hispanic or Latino	-	8 (5.9)	-	8 (5.0)
Not Hispanic or Latino	25 (100.0)	126 (93.3)	7 (100.0)	151 (94.4)
NA	-	1 (0.7)	-	1 (0.6)
Race, N (%)				
N	25 (100.0)	135 (100.0)	7 (100.0)	160 (100.0)
Asian	3 (12.0)	17 (12.6)	1 (14.3)	21 (13.1)
Black or African American	1 (4.0)	4 (3.0)	-	5 (3.1)
White	21 (84.0)	110 (81.5)	6 (85.7)	130 (81.3)
Other	-	1 (0.7)	-	1 (0.6)
NA	-	3 (2.2)	-	3 (1.9)

Patients may be summarised under more than one treatment if they switched regimen during the study.
SD: standard deviation.

	Once weekly	Twice weekly	Three times weekly	Total
Blood type, N (%)				
N	25 (100.0)	135 (100.0)	7 (100.0)	160 (100.0)
A	8 (32.0)	38 (28.1)	2 (28.6)	44 (27.5)
B	2 (8.0)	15 (11.1)	-	17 (10.6)
AB	-	6 (4.4)	-	6 (3.8)
O	7 (28.0)	36 (26.7)	2 (28.6)	44 (27.5)
Missing	8 (32.0)	40 (29.6)	3 (42.9)	49 (30.6)

Haemophilia and treatment history (all ages)

The details of haemophilia treatment, bleeding episodes, inhibitors and genotype were transferred from NN7088-3859 (pathfinder2) and NN7088-3885 (pathfinder5) for the patients when they transferred to pathfinder8 trial.

All 160 patients included in the trial were male and had severe congenital haemophilia A (FVIII activity <1%) according to medical records. All patients were previously treated with N8-GP and had no history of inhibitors. In total, 72 patients had relatives with haemophilia A. None of the patients enrolled had clinical suspicion of inhibitors.

Prior to enrolment in the previous trials (NN7088-3859 (pathfinder2) and NN7088-3885 (pathfinder5)), 134 patients (83.8%) were on prophylaxis treatment; 13 patients used plasma derived FVIII products and 121 used recombinant products. The remaining 26 patients (16.3%) were on on-demand treatment. Mean (SD) number of bleeding episodes within the last 12 months were 7.3 (23.7) for patients on prophylaxis treatment and 32.1 (24.7) for patients on on-demand treatment. Of total 160 patients, 50 patients had undergone surgeries during last 5 years.

Table 20: Trial 4410 Haemophilia and inhibitor history - full analysis set

	Once weekly	Twice weekly	Three times weekly	Total
Number of patients	25	135	7	160
History of haemophilia A among relatives, N (%)				
N	25 (100.0)	135 (100.0)	7 (100.0)	160 (100.0)
Yes	14 (56.0)	59 (43.7)	1 (14.3)	72 (45.0)
No	10 (40.0)	71 (52.6)	6 (85.7)	82 (51.3)
Unknown	1 (4.0)	5 (3.7)	-	6 (3.8)
Relatives with haemophilia A and inhibitors*, N (%)				
N	14 (100.0)	67 (100.0)	1 (100.0)	80 (100.0)
Maternal grandfather	2 (14.3)	9 (13.4)	-	11 (13.8)
Maternal grandparents brothers	-	3 (4.5)	-	3 (3.8)
Maternal uncle	2 (14.3)	10 (14.9)	-	12 (15.0)
None	3 (21.4)	23 (34.3)	-	25 (31.3)
Siblings / cousins	7 (50.0)	22 (32.8)	1 (100.0)	29 (36.3)
Clinical suspicion of inhibitors, N (%)				
N	25 (100.0)	135 (100.0)	7 (100.0)	160 (100.0)
No	25 (100.0)	135 (100.0)	7 (100.0)	160 (100.0)
Number of recovery tests within the last 8 years				
N	25	77	3	101
Mean (SD)	4.2 (3.7)	4.3 (6.8)	3.0 (3.6)	4.4 (6.2)
Median	3.0	1.0	2.0	2.0
Min ; Max	0.0 ; 13.0	0.0 ; 44.0	0.0 ; 7.0	0.0 ; 44.0
Number of inhibitor tests within the last 8 years				
N	25	78	3	102
Mean (SD)	9.4 (5.7)	9.0 (6.3)	11.0 (7.8)	9.0 (6.2)
Median	8.0	7.0	15.0	7.0
Min ; Max	2.0 ; 22.0	2.0 ; 37.0	2.0 ; 16.0	2.0 ; 37.0

Patients may be summarised under more than one treatment if they switched regimen during the study.
* N refers to the number of relatives with haemophilia in total.
SD: standard deviation.

Table 21: Trial 4410 Treatment history - full analysis set (all ages)

	Once weekly	Twice weekly	Three times weekly	Total
Number of patients	25	135	7	160
Type of current treatment, N (%)				
N	25 (100.0)	135 (100.0)	7 (100.0)	160 (100.0)
On-demand Regimen	5 (20.0)	22 (16.3)	-	26 (16.3)
Prophylaxis Regimen	20 (80.0)	113 (83.7)	7 (100.0)	134 (83.8)
Previous prophylaxis patients:				
Months on prophylaxis				
N	20	113	7	134
Mean (SD)	110.9 (92.5)	77.8 (72.5)	81.9 (66.1)	81.1 (75.7)
Median	61.5	49.0	72.0	50.0
Min ; Max	3.0 ; 312.0	1.0 ; 345.0	14.0 ; 199.0	1.0 ; 345.0
Dose level (U/kg)				
N	20	113	7	134
Mean (SD)	25.6 (9.3)	30.9 (11.2)	31.1 (13.4)	30.2 (11.1)
Median	24.5	30.0	28.6	28.6
Min ; Max	5.6 ; 42.3	6.0 ; 60.0	10.0 ; 50.0	5.6 ; 60.0
Frequency of dosing, N (%)				
N	20 (100.0)	113 (100.0)	7 (100.0)	134 (100.0)
Every 2nd day	5 (25.0)	26 (23.0)	1 (14.3)	32 (23.9)
Every 3rd day	3 (15.0)	18 (15.9)	2 (28.6)	20 (14.9)
Every 4th day	1 (5.0)	1 (0.9)	-	2 (1.5)
Every 7th day	-	1 (0.9)	-	1 (0.7)
Other	11 (55.0)	67 (59.3)	4 (57.1)	79 (59.0)
FVIII product given, N (%)				
N	20 (100.0)	113 (100.0)	7 (100.0)	134 (100.0)

Patients may be summarised under more than one treatment if they switched regimen during the study.
* If less than 12 months on prophylaxis, the annual number of bleeding episodes has been imputed.
** If less than 12 months on on-demand, the annual number of bleeding episodes has been imputed.
Vaccinations are recorded in concomitant medications. Planned vaccinations are recorded in concomitant medication at time of vaccination.
SD: standard deviation.

Continued...

	Once weekly	Twice weekly	Three times weekly	Total
Has patient switched FVIII product since diagnosis of haemophilia A, N (%)				
N	5 (100.0)	19 (100.0)	-	23 (100.0)
Yes	5 (100.0)	19 (100.0)	-	23 (100.0)
Surgeries (all patients):				
Surgeries during last 5 years, N (%)				
N	11 (100.0)	41 (100.0)	2 (100.0)	50 (100.0)
Yes	11 (100.0)	41 (100.0)	2 (100.0)	50 (100.0)
Vaccinations (all patients):				
Vaccinations during last 12 months, N (%)				
N	25 (100.0)	78 (100.0)	3 (100.0)	102 (100.0)
Yes	1 (4.0)	13 (16.7)	1 (33.3)	15 (14.7)
No	24 (96.0)	65 (83.3)	2 (66.7)	87 (85.3)
Planned vaccinations 12 months from screening, N (%)				
N	25 (100.0)	78 (100.0)	3 (100.0)	102 (100.0)
Yes	-	9 (11.5)	1 (33.3)	10 (9.8)
No	25 (100.0)	69 (88.5)	2 (66.7)	92 (90.2)

Patients may be summarised under more than one treatment if they switched regimen during the study.
* If less than 12 months on prophylaxis, the annual number of bleeding episodes has been imputed.
** If less than 12 months on on-demand, the annual number of bleeding episodes has been imputed.
Vaccinations are recorded in concomitant medications. Planned vaccinations are recorded in concomitant medication at time of vaccination.
SD: standard deviation.

Trial ID: NN7088-3908

The trial population consisted of 82 male paediatric patients with a mean age of 10.2 months (range: 0−58 months) at baseline. The mean body weight and height of all patients were 8.9 kg (range: 2.9−15.7 kg) and 70.3 cm (range: 48-105.5 cm), respectively. The majority of the patients were white (61%); the second largest group was Asian (30%).

At baseline, the mean age was 10.2 months, the median age was 8.0 months, and the age range was from 0 to 58 months. Patients from 14 different countries participated, including 18 patients (22.2%)

from United States, 12 patients (14.8%) from Thailand, and 11 patients (13.6%) from Malaysia. Seven (7) patients (8.6%) were Hispanic or Latino, while the remaining 74 patients (91.4%) were of other ethnicity. Forty-nine (49) patients (60.5%) were White, 24 patients (29.6%) were Asian, 2 patients (2.5%) were Black or African American, and 6 patients (7.4%) were of different than mentioned race**.**

Table 22: Trial 3908 baseline demographics - full analysis set

	Pre-prophylaxis	Prophylaxis	Total
Number of patients	55	69	81
Age at baseline (months)			
N	55	69	81
Mean (SD)	5.2 (4.9)	11.3 (11.5)	10.2 (11.0)
Median	5.0	9.0	8.0
Min ; Max	0 ; 17	0 ; 58	0 ; 58
Country, N (%)			
N	55 (100.0)	69 (100.0)	81 (100.0)
Australia	5 (9.1)	4 (5.8)	5 (6.2)
Austria	2 (3.6)	4 (5.8)	5 (6.2)
Bulgaria	3 (5.5)	3 (4.3)	3 (3.7)
Canada	1 (1.8)	1 (1.4)	1 (1.2)
Germany	-	1 (1.4)	1 (1.2)
Greece	4 (7.3)	4 (5.8)	4 (4.9)
Israel	9 (16.4)	8 (11.6)	9 (11.1)
Italy	1 (1.8)	1 (1.4)	1 (1.2)
Japan	2 (3.6)	2 (2.9)	3 (3.7)
Malaysia	7 (12.7)	9 (13.0)	11 (13.6)
Spain	3 (5.5)	4 (5.8)	6 (7.4)
Taiwan	1 (1.8)	2 (2.9)	2 (2.5)
Thailand	2 (3.6)	12 (17.4)	12 (14.8)
United States	15 (27.3)	14 (20.3)	18 (22.2)
Ethnicity, N (%)			
N	55 (100.0)	69 (100.0)	81 (100.0)
Hispanic or Latino	2 (3.6)	6 (8.7)	7 (8.6)
Not Hispanic or Latino	53 (96.4)	63 (91.3)	74 (91.4)
Race, N (%)			
N	55 (100.0)	69 (100.0)	81 (100.0)
Asian	10 (18.2)	22 (31.9)	24 (29.6)
Black or African American	2 (3.6)	2 (2.9)	2 (2.5)
Other	2 (3.6)	5 (7.2)	6 (7.4)
White	41 (74.5)	40 (58.0)	49 (60.5)

SD: standard deviation.
Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns, with data from the relevant period.

Table 23: Trial 3908 Body measurements at baseline - full analysis set

	Pre-prophylaxis	Prophylaxis	Total
Number of patients	55	69	81
Age at baseline (months)			
N	55	69	81
Mean (SD)	5.2 (4.9)	11.3 (11.5)	10.2 (11.0)
Median	5.0	9.0	8.0
Min ; Max	0.0 ; 17.0	0.0 ; 58.0	0.0 ; 58.0
Height (cm)			
N	50	64	75
Mean (SD)	64.4 (10.2)	71.7 (13.3)	70.3 (13.2)
Median	65.0	73.0	71.0
Min ; Max	48.0 ; 82.0	48.0 ; 105.5	48.0 ; 105.5
Missing	5	5	6
Body weight (kg)			
N	55	69	81
Mean (SD)	7.8 (2.8)	9.2 (2.9)	8.9 (3.0)
Median	8.5	9.6	9.5
Min ; Max	2.9 ; 12.9	2.9 ; 15.7	2.9 ; 15.7
BMI (kg/m^2)			
N	50	64	75
Mean (SD)	19.0 (7.0)	18.6 (6.4)	18.4 (6.1)
Median	17.2	17.0	17.0
Min ; Max	11.4 ; 51.6	12.7 ; 51.6	11.4 ; 51.6
Missing	5	5	6

Haemophilia and treatment history at baseline

Out of 81 male patients included in the trial, 75 patients and 6 patients were with FVIII activity level =1% respectively according to the medical records or measurements of FVIII activity at baseline. Forty-five (45) patients had relatives with a history of haemophilia A and 6 patients had relatives with a history of FVIII inhibitors.

Information on genotype was available from 63 patients. Intron 22 mutations (27 patients), missense mutations (11 patients), and small deletions (8 patients) were the three most frequent gene abnormalities causing the haemophilia condition.

Table 24: Trial 3908 Haemophilia history - full analysis set

	Pre-prophylaxis	Prophylaxis	Total
Number of patients	55	69	81
FVIII level (%) from medical history in ranges*, N (%)			
N	55 (100.0)	69 (100.0)	81 (100.0)
<1	52 (94.5)	63 (91.3)	75 (92.6)
>=1	3 (5.5)	6 (8.7)	6 (7.4)
FVIII level (IU/mL) at screening**			
N	4	5	6
Mean (SD)	0.005 (0.002)	0.005 (0.002)	0.005 (0.002)
Median	0.004	0.005	0.004
Min ; Max	0.003 ; 0.007	0.003 ; 0.008	0.003 ; 0.008
History of haemophilia A among relatives, N (%)			
N	55 (100.0)	69 (100.0)	81 (100.0)
Yes	36 (65.5)	36 (52.2)	45 (55.6)
No	19 (34.5)	32 (46.4)	35 (43.2)
Unknown	-	1 (1.4)	1 (1.2)
Relatives with haemophilia A***, N (%)			
N	36 (100.0)	36 (100.0)	45 (100.0)
Maternal Grandfather	6 (16.7)	5 (13.9)	6 (13.3)
Maternal Grandfather-Maternal Uncle	1 (2.8)	-	1 (2.2)
Maternal Uncle	5 (13.9)	7 (19.4)	9 (20.0)
Maternal Uncle-Siblings / Cousins	1 (2.8)	1 (2.8)	1 (2.2)
Other relation: Both His Mother And Maternal Grandmother Have A Biological Profile Of Hemophilia A Conductor. Molecular Biology Analysis Of Factor Viii Gene Has Been Initiated. Results Pending.	-	1 (2.8)	1 (2.2)
Other relation: Mother Has Strong Family History Of Haemophilia: Maternal Uncle And Maternal Cousin	1 (2.8)	1 (2.8)	1 (2.2)

SD: standard deviation.
Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns, with data from the relevant period.
* FVIII level from medical history is not available for all patients.
** Plasma activities below lower limit of quantification (LLOQ) are set to half of LLOQ.
*** N refers to the number patients with answer 'Yes' to the question.

Continued...

	Pre-prophylaxis	Prophylaxis	Total
Has Severe Haemophilia A.			
Other relation: Mother Tested And Found To Be Hemophilia A Carrier-Siblings / Cousins	1 (2.8)	1 (2.8)	1 (2.2)
Other relation: Mother's Cousins-Maternal Grandfather	1 (2.8)	1 (2.8)	1 (2.2)
Siblings / Cousins	17 (47.2)	15 (41.7)	20 (44.4)
Siblings / Cousins-Maternal Grandfather	2 (5.6)	2 (5.6)	2 (4.4)
Siblings / Cousins-Maternal Grandparents Brothers	1 (2.8)	1 (2.8)	1 (2.2)
Siblings / Cousins-Maternal Uncle	-	1 (2.8)	1 (2.2)
Relatives with inhibitors***, N (%)			
N	9 (100.0)	9 (100.0)	10 (100.0)
Maternal Grandfather: Positive Inhibitor	1 (11.1)	1 (11.1)	1 (10.0)
Maternal Uncle: Positive Inhibitor	1 (11.1)	1 (11.1)	1 (10.0)
Relatives Other: Positive Inhibitor	1 (11.1)	1 (11.1)	1 (10.0)
Siblings/Cousins: Positive Inhibitor	6 (66.7)	6 (66.7)	7 (70.0)

Numbers analysed

Trial ID: NN7088-3885

A total of 68 patients were exposed to N8-GP with a total of 32138 EDs and a total trial time of 305.72 years (Table 25). In general, patients in the 6-11 year group had a bit higher exposure compared to patients in the 0-5 year age group (166.73 vs. 138.98 years).

The safety analysis set and the FAS were identical and included all 68 exposed patients. However, one patient was excluded from the analysis of the secondary endpoint ‘Incidence of inhibitory antibodies against FVIII ≥0.6 BU during the compiled main and interim extension phase of the trial’ because this patient was found to be wrongly included due to inhibitory antibodies.

Table 25: N8-GP exposure – full analysis set

	Younger children (0 - 5 years)	Older children (6 - 11 years)	Total
Number of patients	34	34	68
Total time in trial (years)	138.98	166.73	305.72
Total number of exposure days	14596	17542	32138
Total number of doses per patient			
N	34	34	68
Mean (SD)	429.6 (180.2)	516.9 (18.8)	473.3 (134.5)
Median	483.5	517.5	504.5
Min ; Max	2.0 ; 582.0	484.0 ; 560.0	2.0 ; 582.0
Total number of exposure days per patient			
N	34	34	68
Mean (SD)	429.3 (180.1)	515.9 (18.6)	472.6 (134.3)
Median	482.5	517.0	504.5
Min ; Max	2.0 ; 582.0	484.0 ; 560.0	2.0 ; 582.0
Total number of prophylaxis doses per patient			
N	34	34	68
Mean (SD)	424.2 (178.1)	506.6 (19.6)	465.4 (132.4)
Median	480.5	504.5	491.5
Min ; Max	2.0 ; 577.0	474.0 ; 539.0	2.0 ; 577.0
Total number of doses used for treatment of bleed per patient			
N	26	29	55
Mean (SD)	6.7 (5.1)	11.4 (8.9)	9.2 (7.7)
Median	4.0	10.0	7.0
Min ; Max	1.0 ; 18.0	1.0 ; 31.0	1.0 ; 31.0

Trial ID: NN7088-4410

A total of 160 patients were exposed to N8-GP, with a total of 28698 EDs and a total trial time of 298.2 years during the current pathfinder8 trial.

The safety analysis set and the full analysis set were identical and consisted of all dosed patients. A total of 160 patients were included in these analysis sets. None of the patients or data points were excluded from the full analysis set.

Table 26: N8-GP exposure in trial 4410 – full analysis set

	Once weekly	Twice weekly	Three times weekly	Total
Number of patients	25	135	7	160
Total time in trial (years)	46.2	241.4	8.3	298.2
Total number of doses per patient*				
N	25	135	7	160
Mean (SD)	102.4 (31.1)	184.9 (51.7)	174.1 (100.1)	179.6 (55.2)
Median	105.0	208.0	196.0	207.0
Min ; Max	37 ; 209	30 ; 248	30 ; 312	30 ; 312
Total time in trial per patient (days)				
N	25	135	7	160
Mean (SD)	675.0 (152.4)	653.0 (178.0)	433.0 (255.6)	680.8 (148.7)
Median	729.0	732.0	469.0	733.0
Min ; Max	228 ; 792	105 ; 813	71 ; 726	137 ; 862
Total number of exposure days per patient				
N	25	135	7	160
Mean (SD)	102.2 (30.6)	184.6 (51.6)	173.9 (99.9)	179.4 (55.1)
Median	105.0	208.0	196.0	206.0
Min ; Max	37 ; 206	30 ; 246	30 ; 312	30 ; 312
Total number of prophylaxis doses per patient				
N	25	135	7	160
Mean (SD)	95.2 (21.3)	181.0 (51.3)	170.7 (97.5)	175.1 (54.8)
Median	103.0	206.0	194.0	204.5
Min ; Max	31 ; 110	30 ; 238	30 ; 309	30 ; 309
Total number of doses used for treatment of bleed per patient				
N	10	61	3	72
Mean (SD)	14.4 (32.3)	4.7 (4.8)	5.3 (4.9)	6.2 (12.8)
Median	4.5	3.0	3.0	3.0
Min ; Max	1 ; 106	1 ; 20	2 ; 11	1 ; 106
Total time in major surgery period (days)				
N**	4	13	0	17
Mean (SD)	12.0 (5.5)	19.2 (35.0)	0 (0)	17.5 (30.5)
Median	10.0	9.0	0	9.0
Min ; Max	8 ; 20	2 ; 131	0 ; 0	2 ; 131
Total number of doses during the period of major surgery				
N**	4	13	0	17
N+	31	179	0	210
Mean (SD)	7.8 (2.6)	13.8 (21.4)	0 (0)	12.4 (18.8)
Median	8.5	7.0	0	8.0
Min ; Max	4 ; 10	2 ; 81	0 ; 0	2 ; 81

Patients may be summarised under more than one treatment if they switched regimen during the study.
Total number of exposure days in trial is number of days with doses (excluding surgery).
*Total number of doses includes all doses given.
N is the number of patients.
+ N is the number of doses given in the surgery period.
** N is the number of surgeries.
SD: standard deviation.
Patient [redacted] in once weekly dosing regimen, had 92 bleeds out of 123 bleeds in that group.

Trial ID: NN7088-3908

A total of 81 patients were exposed to N8-GP with a mean and median of 207.0 and 154.0 doses per patient, respectively, ranging from 1 to 792.0 doses per patient. The vast majority of treatment with N8-GP was provided while patients were on prophylaxis where the mean number of EDs per patient was 235.4 EDs, while patients on pre-prophylaxis had a mean of 7.8 Eds.

Out of 82 enrolled patients, 1 patient was not exposed to N8-GP and not included in the analyses sets. The safety analysis set and the full analysis set were identical and consisted of 81 patients exposed to

N8-GP. No patients were excluded from the full analyses set. One (1) patient who was enrolled in the trial having a high-titer positive inhibitor test at baseline was excluded from analyses of FVIII inhibitor incidence. For each patient, collected data up until and including the last visit was part of the data base lock (10-Jan-2022) and was used in the statistical analyses. Out of exposed 81 patients, 3 patients were registered as withdrawn in EDC as they did not get to visit 14 before the trial was closed, but they were considered as study completers and were included for the results analysis.

Data collected during pre-prophylaxis and prophylaxis was analysed separately and as a total for all endpoints. Data collected during ITI treatment was analysed separately for selected endpoints only. All patients reached end of trial except 2 ITI patients whose LPLV date has been extended to 17 June 2023. A CTR addendum was prepared for these 2 ITI patients after they completed the trial.

Table 27: N8-GP exposure - main + extension - full analysis set

	Pre-prophylaxis	Prophylaxis	Total
Number of patients	55	69	81
Total number of doses per patient*			
N	55	69	81
Mean (SD)	8.1 (6.1)	236.6 (208.2)	207.0 (208.7)
Median	7.0	177.0	154.0
Min ; Max	1.0 ; 24.0	7.0 ; 792.0	1.0 ; 792.0
Total number of exposure days per patient			
N	55	69	81
Mean (SD)	7.8 (6.0)	235.4 (207.7)	205.8 (208.2)
Median	7.0	175.0	153.0
Min ; Max	1.0 ; 22.0	7.0 ; 791.0	1.0 ; 791.0
Treatment period per patient (years)			
N	55	69	81
Mean (SD)	0.5 (0.4)	2.9 (2.1)	2.8 (2.2)
Median	0.4	2.9	2.5
Min ; Max	0.0 ; 1.9	0.1 ; 7.2	0.0 ; 7.4
Total number of prophylaxis doses per patient			
N	0	69	69
Mean (SD)	- (-)	236.6 (208.2)	236.6 (208.2)
Median	-	177.0	177.0
Min ; Max	- ; -	7.0 ; 792.0	7.0 ; 792.0
Total number of pre-prophylaxis doses per patient			
N	55	0	55
Mean (SD)	8.1 (6.1)	- (-)	8.1 (6.1)
Median	7.0	-	7.0
Min ; Max	1.0 ; 24.0	- ; -	1.0 ; 24.0
Total number of doses used for treatment of bleed per patient			
N	48	60	75
Mean (SD)	4.9 (4.3)	7.9 (9.3)	9.5 (10.9)
Median	3.0	5.5	6.0
Min ; Max	1.0 ; 16.0	1.0 ; 64.0	1.0 ; 77.0
Total number of doses used for surgery			
N	9	16	25
Mean (SD)	3.1 (2.4)	5.3 (4.4)	4.5 (3.9)
Median	2.0	3.5	3.0
Min ; Max	1.0 ; 7.0	1.0 ; 16.0	1.0 ; 16.0

Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns, with data from the relevant period.
* Total number of doses includes all doses given.
N: number of patients
SD: standard deviation.

Outcomes and estimation

Outcomes and estimation

Trial ID: NN7088-3885 – outcomes and estimation

Table 28 – Trial 3885 Annualised bleeding rate - full analyses set (main & extension)

	Younger children (0-5 years)	Older children (6-11 years)	Total
Number of patients	34	34	68
Number of patients with bleeds, N(%)	26 (76.5)	29 (85.3)	55 (80.9)
Number of bleeds	108	222	330
Bleeds per patient (min ; max)	0; 11	0; 29	0; 29
Mean treatment period (years)	4.088	4.904	4.496
Individual ABRs			
N	34	34	68
Mean (SD)	3.05 (9.74)	1.34 (1.36)	2.20 (6.95)
Median	0.61	0.93	0.81
Interquartile range	0.20; 1.19	0.20; 2.11	0.20; 1.62
Min ; max	0.00;45.66	0.00; 6.16	0.00;45.66
Poisson estimate of ABR	0.78	1.33	1.08
95% CI	0.46; 1.30	0.93; 1.91	0.81; 1.44
Negative binomial estimate of ABR	0.86	1.34	1.14
95% CI	0.57; 1.29	0.96; 1.88	0.87; 1.49
LOCF sensitivity analysis			
Number of patients with less than 30 days of exposure	4	0	4
Number of patients with LOCF	6	0	6
Bleeds per patient (min ; max)	0; 13	0; 29	0; 29
Mean treatment period (years)	4.147	4.904	4.526
Poisson estimate of ABR	1.09	1.33	1.22
95% CI	0.54; 2.19	0.74; 2.39	0.79; 1.87
Negative binomial estimate of ABR	2.93	1.34	2.04
95% CI	1.74; 4.92	0.84; 2.16	1.41; 2.95

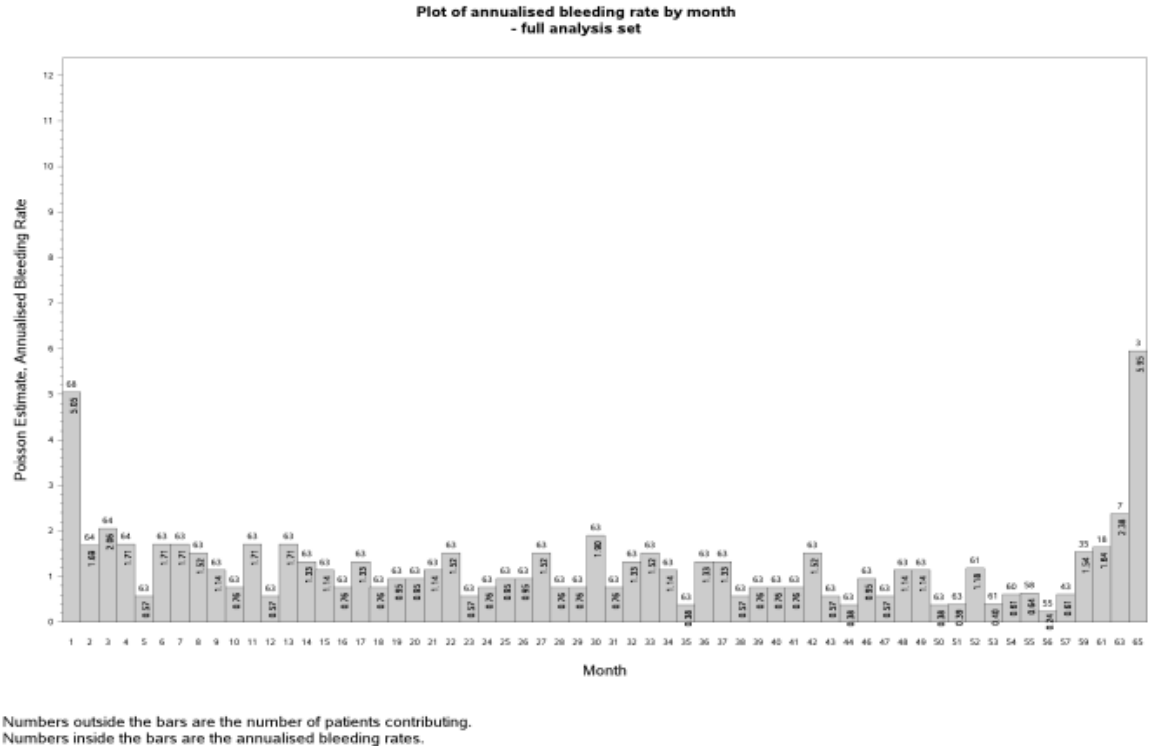
ABR: Annualised bleeding rate.
LOCF: Last observation carried forward.
Based on a Poisson regression model with age group as a factor allowing over-dispersion and using the log of treatment duration as an offset.
A sensitivity analysis was carried out using the negative binomial model with the log of treatment duration as an offset.

Table 29: Trial 3885 - Annualised bleeding rate during trial compared to bleeding rate prior to inclusion in trial 3885

	Younger children (0 - 5 years)	Older children (6 - 11 years)	Total
Number of patients	31	34	65
Historical ABRs*			
Mean ABR	4.65	7.94	6.37
ABRs during trial			
Mean ABR	3.30	1.34	2.28

ABR: Annualised bleeding rate.
* Bleeding rate during last 12 months prior to trial

Figure 1 - 3885 Plot of annualised bleeding rate by month - full analysis set



Numbers outside the bars are the number of patients contributing.
Numbers inside the bars are the annualised bleeding rates.

Target joints

Six (6) of the 13 patients aged <12 years who had target joints at baseline did not have any target joint bleeds at the EOT. Of these 6 patients, 4 were from the age group of 0-5 years and 2 from 6-11 years age-group.

Haemostatic effect

The haemostatic success rate (including missing data as failures) for treatment of bleeds was 79% in the main phase of the trial and 82% in the main+extension phase.

Table 30: Trial 3885 Haemostatic response - full analysis set

	Younger children (0 - 5 years)	Older children (6 - 11 years)	Total
Number of patients	34	34	68
Number of patients with bleeds, N(%)	26 (76.5)	29 (85.3)	55 (80.9)
Number of patients with no bleeds, N(%)	8 (23.5)	5 (14.7)	13 (19.1)
Number of bleeds	108	222	330
Haemostatic response, N(%)			
N	108 (100.0)	222 (100.0)	330 (100.0)
Excellent	47 (43.5)	96 (43.2)	143 (43.3)
Good	48 (44.4)	74 (33.3)	122 (37.0)
Moderate	9 (8.3)	44 (19.8)	53 (16.1)
None	2 (1.9)	2 (0.9)	4 (1.2)
Missing	2 (1.9)	6 (2.7)	8 (2.4)
Success/failure, N(%)			
N	106 (100.0)	216 (100.0)	322 (100.0)
Success	95 (89.6)	170 (78.7)	265 (82.3)
Failure	11 (10.4)	46 (21.3)	57 (17.7)
Success/failure, N(%) (incl. missing as failure)			
N	108 (100.0)	222 (100.0)	330 (100.0)
Success	95 (88.0)	170 (76.6)	265 (80.3)
Failure	13 (12.0)	52 (23.4)	65 (19.7)
Success rate			
Rate	88.3	80.1	83.7
95% CI	76.3 ; 94.6	71.5 ; 86.6	77.0 ; 88.8
Success rate (incl. missing as failure)			
Rate	87.1	77.7	81.6
95% CI	76.4 ; 93.4	69.5 ; 84.2	75.2 ; 86.7

Analysed using logistic regression accounting for repeated measures within patient and assuming compound symmetry working correlation.
Only bleeds treated with N8-GP are included.

Consumption

Table 1: 3885 Consumption of N8-GP - full analysis set

	Younger children (0 - 5 years)	Older children (6 - 11 years)	Total
Number of patients	34	34	68
Consumption used for treatment* per year per patient** (IU/kg/year)			
N	34	34	68
Mean (SD)	6778.6 (1039)	6760.4 (181.8)	6769.5 (740.1)
Median	6812.0	6767.9	6784.6
Min ; Max	3121.8 ; 9131.3	6265.3 ; 7168.3	3121.8 ; 9131.3
Consumption used for treatment* per month per patient** (IU/kg/month)			
N	34	34	68
Mean (SD)	564.9 (86.6)	563.4 (15.1)	564.1 (61.7)
Median	567.7	564.0	565.4
Min ; Max	260.1 ; 760.9	522.1 ; 597.4	260.1 ; 760.9
Average prophylaxis dose*** (IU/kg)			
N	14442	17243	31685
Mean (SD)	65.4 (7.5)	64.1 (5.3)	64.7 (6.4)
Median	66.5	64.0	65.1
Min ; Max	11.0 ; 258.1	8.3 ; 114.6	8.3 ; 258.1
Average dose for treatment of bleed from start to stop of bleed+ (IU/kg/bleed)			
N	108	222	330
Mean (SD)	102.8 (81.0)	91.0 (58.3)	94.9 (66.7)
Median	68.8	66.9	68.2
Min ; Max	44.9 ; 564.9	29.7 ; 344.8	29.7 ; 564.9
Average dose for treatment of bleed using <=2 doses+ (IU/kg/bleed)			
N	95	196	291
Mean (SD)	78.4 (26.8)	73.6 (25.4)	75.1 (25.9)
Median	68.3	65.4	66.7
Min ; Max	44.9 ; 145.5	29.7 ; 146.8	29.7 ; 146.8

*Consumption used for treatment includes all doses given (prophylaxis, treatment of bleed, minor surgery and pharmacokinetic)
**N is number of patients
***N is number of doses
+N is number of bleeds

Table 2Trial 3885 N8-GP exposure - full analysis set

	Younger children (0 - 5 years)	Older children (6 - 11 years)	Total
Number of patients	34	34	68
Total number of doses per patient			
N	34	34	68
Mean (SD)	429.6 (180.2)	516.9 (18.8)	473.3 (134.5)
Median	483.5	517.5	504.5
Min ; Max	2.0 ; 582.0	484.0 ; 560.0	2.0 ; 582.0
Total number of exposure days per patient			
N	34	34	68
Mean (SD)	429.3 (180.1)	515.9 (18.6)	472.6 (134.3)
Median	482.5	517.0	504.5
Min ; Max	2.0 ; 582.0	484.0 ; 560.0	2.0 ; 582.0
Total exposure time per patient (days)			
N	34	34	68
Mean (SD)	1493.1 (624.7)	1791.1 (73.2)	1642.1 (466.3)
Median	1692.5	1786.5	1774.0
Min ; Max	14.0 ; 1971.0	1675.0 ; 1989.0	14.0 ; 1989.0
Total number of prophylaxis doses per patient			
N	34	34	68
Mean (SD)	424.2 (178.1)	506.6 (19.6)	465.4 (132.4)
Median	480.5	504.5	491.5
Min ; Max	2.0 ; 577.0	474.0 ; 539.0	2.0 ; 577.0
Total number of doses used for treatment of bleed per patient			
N	26	29	55
Mean (SD)	6.7 (5.1)	11.4 (8.9)	9.2 (7.7)
Median	4.0	10.0	7.0
Min ; Max	1.0 ; 18.0	1.0 ; 31.0	1.0 ; 31.0
Total number of doses used for treatment of suspected severe bleed			
N	4	6	10
Mean (SD)	1.0 (0.0)	1.3 (0.8)	1.2 (0.6)
Median	1.0	1.0	1.0
Min ; Max	1.0 ; 1.0	1.0 ; 3.0	1.0 ; 3.0

Surgeries

Patients could undergo minor surgeries, dental extractions and placement of central venous access ports while participating in this trial. Excessive bleeding during the surgery was to be mitigated by administering an extra dose of N8-GP equivalent to the dose administered for a severe bleeding episode, or aligned to local practice. Patients in need of major surgery were to be withdrawn from the trial.

Table 3: **Minor surgery - full analysis set**

	Younger children (0 - 5 years)	Older children (6 - 11 years)	Total
Number of patients	34	34	68
Description of surgery, N (%)			
N	19 (100.0)	26 (100.0)	45 (100.0)
Adenoidectomy	-	1 (3.8)	1 (2.2)
Baby tooth extraction	-	1 (3.8)	1 (2.2)
Bilateral myringotomy tube placement	1 (5.3)	-	1 (2.2)
Dental extraction	1 (5.3)	12 (46.2)	13 (28.9)
Dental filling	2 (10.5)	1 (3.8)	3 (6.7)
Dental filling (two teeth)	1 (5.3)	-	1 (2.2)
Dental removal	-	1 (3.8)	1 (2.2)
Emergency circumcision	1 (5.3)	-	1 (2.2)
Epigastric hernia cure	-	1 (3.8)	1 (2.2)
Extensive dental procedure - multiple caries filled of several teeth.	1 (5.3)	-	1 (2.2)
Minor surgery (needle aspiration from upper eyelid)	-	1 (3.8)	1 (2.2)
Minor surgery - cyst excision	-	1 (3.8)	1 (2.2)
Minor surgery-suture	-	1 (3.8)	1 (2.2)
Minor tooth extraction	-	1 (3.8)	1 (2.2)
Nevus removal	-	1 (3.8)	1 (2.2)
One tooth extracted (dentoaveolar procedure) and one root canal	1 (5.3)	-	1 (2.2)
Port a cath removal	-	1 (3.8)	1 (2.2)
Port-a-cath removal	-	2 (7.7)	2 (4.4)
Portacath removal	1 (5.3)	-	1 (2.2)
Removal and insertion of a port-a-cath	1 (5.3)	-	1 (2.2)
Removal of port-a -cath	1 (5.3)	-	1 (2.2)
Removal of single lumen titanium port (right)	1 (5.3)	-	1 (2.2)
Simple extraction of teeth b and i; pulp therapy; space maintainers, crown insertion	1 (5.3)	-	1 (2.2)
Social circumcision	1 (5.3)	-	1 (2.2)
Tooth extraction	2 (10.5)	-	2 (4.4)
Tooth extraction (one tooth)	-	1 (3.8)	1 (2.2)
Tooth extraction (two teeth)	2 (10.5)	-	2 (4.4)
Tooth extraxtion	1 (5.3)	-	1 (2.2)
Treatment, N (%)			
N	19 (100.0)	26 (100.0)	45 (100.0)
N8-GP 50-75 U/kg Prophylaxis	19 (100.0)	26 (100.0)	45 (100.0)

Patient reported outcomes

Total change scores [change, (SD); N] indicated an improvement in QoL with haemophilia (HAEMO-QOL) for patients aged 4–7 years [-18.7 (17.7); 11] and their parents [-9.7 (24.2); 15]. A similar trend was seen for the patients aged 8–11 years; the total change score was [-7.6 (9.1); 22] compared with their parents [-10.0 (9.7); 20]. Recordings of treatment satisfaction among parents (HEMO SAT) also suggested an improvement in total change score [change, (SD); N]: [-5.8 (15.4); 54].

Trial ID: NN7088-4410 – outcomes and estimation

Annualised bleeding rates

Annualised bleeding rate was estimated including all spontaneous and traumatic bleeding episodes observed during the trial. One (1) surgical bleeding episode occurring in a child during the trial was excluded from the ABR calculation.

In children (<12 years), the median ABR (IQR) for total bleeds was 0.00 (0.00; 0.50) bleeds/patient/year. The median ABRs (IQR) for spontaneous and traumatic bleeds were 0.00 (0.00; 0.00) bleeds/patient/year and 0.00 (0.00; 0.50) bleeds/patient/year. The Poisson-estimated ABRs for children were

- 0.65 [0.27; 1.59]95%CI bleeds/patient/year (total bleeds)
- 0.16 [0.05; 0.55]95% CI bleeds/patient/year (spontaneous bleeds)
- 0.49 [0.20; 1.19]95% CI bleeds/patient/year (traumatic bleeds).

Table 4: **Trial 4410 Annualised bleeding rate (0-11 years) - full analysis set**

	Once weekly	Twice weekly	Three times weekly	Total
Number of patients	0	29	1	29
Number of patients with bleeds, N (%)		14 (48.3)	0 (0.0)	14 (48.3)
Number of observed bleeds		36	0	36
Bleeds per patient (min ; max)		0 ; 13	-	0 ; 13
Mean treatment period (years)***		1.897	0.194	1.904
Annualised bleeding rate				
Individual ABRs				
N		29	1	29
Mean (SD)		0.90 (1.98)	0.00 (-)	0.88 (1.95)
Median		0.00	-	0.00
Interquartile range		0.00 ; 0.50	-	0.00 ; 0.50
Min ; Max		0.00 ; 7.94	-	0.00 ; 7.94
Poisson estimate of ABR		0.65		0.65
95% CI		0.27 ; 1.60		0.27 ; 1.59
Negative binomial estimate of ABR+		0.82		0.80
95% CI		0.40 ; 1.69		0.39 ; 1.65
LOCF sensitivity analysis				
Number of patients with LOCF		3	0	3
Number of bleeds using imputation**		50	0	50
Bleeds per patient (min ; max)**		0 ; 16	0 ; 0	0 ; 16
Mean treatment period (years)***		1.989	0.194	1.996
Poisson estimate of ABR		0.87		0.86
95% CI		0.38 ; 1.98		0.38 ; 1.97
Negative binomial estimate of ABR+		0.90		0.89
95% CI		0.44 ; 1.83		0.44 ; 1.80

The analysis is based on a Poisson regression model with logarithmic prophylaxis duration as offset and allowing for over-dispersion. Over-dispersion will be estimated as Pearson's chi-square statistic divided by the degrees of freedom.
For sub-groups with no bleeds or less than 5 patients, the 95% confidence interval will not be presented.
Patients may be summarised under more than one treatment if they switched regimen during the study.
+ Additional sensitivity analysis based on a negative binomial model.
**For patients withdrawing, the number of bleeding episodes will be imputed up to what could be expected if they had completed the trial.
***For patients withdrawing prematurely, the planned treatment duration is used; for completers, the actual treatment duration is used.
Missing diary period and surgery period is excluded when relevant. Surgery bleeds are excluded.

Haemostatic effect

In the Trial 4410, a total of 36 bleeding episodes were reported in 14 (48.3%) children (aged <12 years) with a haemostatic success rate of 100%. One (1) additional surgical bleeding episode occurring in a child was excluded from the haemostatic success rate calculation. Haemostatic effect by country, race and ethnicity did not show any trend/pattern.

Comparable success rates were observed between children, adolescent and adult patients for all three prophylactic dosing regimens. The total estimated haemostatic response rates for spontaneous and traumatic bleeds (including missing responses considered as failures) were 91.6% and 99.3%, respectively. The most prominent location of bleeds was joints (218 bleeds) followed by skin and muscular (55 bleeds and 36 bleeds, respectively).

In the Trial 4410, of the total 29 children (aged <12 years), only one patient underwent a major surgery during the trial. The haemostatic response for this patient was reported as “good”.

Table 35: Trial 4410 Haemostatic effect of N8-GP (0-11 years) - full analysis set

	Once weekly	Twice weekly	Three times weekly	Total
Number of patients	0	29	1	29
Number of patients with bleeds, N (%)	0 (0.0)	14 (48.3)	0 (0.0)	14 (48.3)
Number of bleeds	0	36	0	36
Haemostatic response, N (%)				
N	0 (0.0)	36 (100.0)	0 (0.0)	36 (100.0)
Excellent	0 (0.0)	22 (61.1)	0 (0.0)	22 (61.1)
Good	0 (0.0)	14 (38.9)	0 (0.0)	14 (38.9)
Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
None	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Success/failure (incl. missing as failure), N (%)				
N	0 (0.0)	36 (100.0)	0 (0.0)	36 (100.0)
Success	0 (0.0)	36 (100.0)	0 (0.0)	36 (100.0)
Failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Success/failure (excl. missing), N (%)				
N	0 (0.0)	36 (100.0)	0 (0.0)	36 (100.0)
Success	0 (0.0)	36 (100.0)	0 (0.0)	36 (100.0)
Failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Success rate (incl. missing as failure)				
Rate		100.0		100.0
95% CI		-		-
Success rate (excl. missing)				
Rate		100.0		100.0

Analysed using logistic regression accounting for repeated measures within subject assuming compound symmetry working correlation, age group is included as a factor and modelling done separately for each treatment regimen. If there are no failures in a subgroup, logistic regression cannot be performed, and a success rate of 100.0% is assigned with CI equal to missing.
Patients may be summarised under more than one treatment if they switched regimen during the study.
A successfully treated bleed is a bleeding episode where the treatment response was excellent or good.
Only patient [redacted] was below 6 years old at baseline (age=[redacted], therefore the two age groups of 0-5 years and 6-11 years are grouped into 0-11 years.
Bleeds treated only with disallowed medication are excluded, and surgery bleeds are also excluded.

Table 36: Number of injections of N8-GP per bleed (per dosing interval, all age groups) - full analysis set

	Once weekly	Twice weekly	Three times weekly	Total
Number of patients	25	135	7	160
Number of patients with bleeds, N(%)	10 (40.0)	61 (45.2)	3 (42.9)	72 (45.0)
Number of bleeds	123	190	14	327
Number of injections to treat the bleed*, N (%)				
N	123 (100.0)	190 (100.0)	14 (100.0)	327 (100.0)
1 injection	110 (89.4)	136 (71.6)	12 (85.7)	258 (78.9)
2 injections	10 (8.1)	39 (20.5)	2 (14.3)	51 (15.6)
3 injections	2 (1.6)	5 (2.6)	-	7 (2.1)
4 injections	-	2 (1.1)	-	2 (0.6)
5 injections	-	3 (1.6)	-	3 (0.9)
6 injections	1 (0.8)	2 (1.1)	-	3 (0.9)
8 injections	-	1 (0.5)	-	1 (0.3)
9 injections	-	1 (0.5)	-	1 (0.3)
10 injections	-	1 (0.5)	-	1 (0.3)
N	123	190	14	327
Mean (SD)	1.2 (0.6)	1.5 (1.3)	1.1 (0.4)	1.4 (1.1)
Median	1.0	1.0	1.0	1.0
Min ; Max	1.0 ; 6.0	1.0 ; 10.0	1.0 ; 2.0	1.0 ; 10.0

Patients may be summarised under more than one treatment if they switched regimen during the study.
* N is the number of bleeds. SD: standard deviation. All bleeds including surgery bleeds are included.
Patient [redacted] in once weekly dosing regimen, had 92 bleeds out of 123 bleeds in that group.

Table 37: Actual N8-GP consumption (per dosing interval, all age groups) - full analysis set

Table 37: Actual N8-GP consumption (per dosing interval, all age groups) - full analysis set

	Once weekly	Twice weekly	Three times weekly	Total
Number of patients	25	128	7	160
Consumption used for treatment* per year per patient (IU/kg/year)				
N	25	135	7	160
Mean (SD)	4050 (468.5)	5424 (859.1)	7740 (710.9)	5220 (828.1)
Median	4055	5377	7972	5315
Min ; Max	2833 ; 5757	2637 ; 7849	6139 ; 8153	2578 ; 7997
Consumption used for treatment* per month per patient (IU/kg/year)				
N	25	135	7	160
Mean (SD)	337.5 (39.0)	452.0 (46.6)	645.0 (59.2)	435.0 (69.0)
Median	337.9	440.1	664.3	442.9
Min ; Max	236.1 ; 479.8	219.7 ; 654.1	511.6 ; 679.4	214.8 ; 666.4
Consumption used for prophylaxis per year per patient (IU/kg/year)				
N	25	135	7	160
Mean (SD)	3878 (296.4)	5320 (565.0)	7646 (877.2)	5110 (821.3)
Median	3921	5202	7922	5221
Min ; Max	2782 ; 4287	2627 ; 7626	5671 ; 8152	2578 ; 7922
Average prophylaxis dose (IU/kg)				
N	25	135	7	160
N**	2351	24434	1195	28013
Mean (SD)	75.2 (5.4)	52.7 (4.2)	52.1 (1.0)	55.9 (9.1)
Median	75.7	51.7	51.9	52.0
Min ; Max	53.9 ; 84.3	43.8 ; 75.5	51.2 ; 54.0	43.8 ; 84.3
Average dose for treatment of bleed (IU/kg/bleed)				
N	10	61	2	72
N+	120	190	14	327
Mean (SD)	91.3 (55.0)	61.9 (59.9)	61.1 (12.0)	68.0 (59.7)
Median	73.6	61.3	56.7	64.9
Min ; Max	25.9 ; 325.0	29.7 ; 375.0	52.0 ; 74.6	25.9 ; 375.0

Patients may be summarised under more than one treatment if they switched regimen during the study. + N is the number of bleeds.
* Consumption used for treatment includes all doses given. Yearly consumption is only calculated for patients with a exposure time of at least 30 days. Missing diary period is excluded when calculating yearly consumption. N: Number of patients.SD: standard deviation.
** N is the number of prophylaxis doses. Patient [redacted] in once weekly dosing regimen, had 92 bleeds out of 120 bleeds in that group.

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Trial ID: NN7088-3908 – outcomes and estimation

Annualized bleeding rate (ABR)

ABR estimates for bleeds observed during main+extension phase in patients on prophylaxis were calculated based on 347 treatment-requiring bleeds observed in 60 (87.0%) of the 69 patients who received prophylaxis. The median ABR was 1.35 (interquartile range: 0.60; 3.50) bleeds/patient/year. The ABR estimate using the negative binomial model was 2.27 (95% CI: 1.71; 3.01) bleeds/patient/year. The ABR estimate using the Poisson regression model was 1.76 (95% CI: 1.26; 2.46) bleeds/patient/year.

Table 38: ABR - main + extension - full analysis set

	Pre-prophylaxis	Prophylaxis	Total
Number of patients	55	69	81
Number of patients with bleeds, N(%)	48 (87.3)	60 (87.0)	75 (92.6)
Number of bleeds	163	347	510
Bleeds per patient (min ; max)	0; 13	0; 57	0; 70
Mean treatment period (years)	0.492	2.858	2.769
Individual ABRs			
N	55	69	81
Mean (SD)	19.37 (50.76)	3.46 (7.10)	9.33 (41.18)
Median	6.52	1.35	1.99
Interquartile range	2.52;13.04	0.60; 3.50	0.93; 5.10
Min ; max	0.00;365.3	0.00;49.81	0.00;365.3
Negative binomial estimate of ABR	6.55	2.27	3.16
95% CI	5.18; 8.27	1.71; 3.01	2.45; 4.06
Poisson estimate of ABR	6.02	1.76	2.27
95% CI	4.44; 8.17	1.26; 2.46	1.69; 3.07
LOCF sensitivity analysis			
Number of patients with less than 30 days of exposure		1	1
Number of patients with LOCF		17	17
Bleeds per patient (min ; max)		0; 57	0; 57
Mean treatment period (years)		3.021	3.021
Negative binomial estimate of ABR		3.09	3.09
95% CI		2.27; 4.21	2.27; 4.21
Poisson estimate of ABR		2.12	2.12
95% CI		1.34; 3.37	1.34; 3.37

LOCF: Last observation carried forward.
Based on a negative binomial model with the log of treatment duration as an offset.
Poisson regression model allowing over-dispersion and using treatment duration as an offset.
Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns.
Bleeds treated with by-passing agents are included.
One patient had a very high ABR of 365.25 because they only had one ED and also one bleed.

Table 39: Haemostatic response - main + extension - full analysis set

	Pre-prophylaxis	Prophylaxis	Total
Number of patients	55	69	81
Number of patients with bleeds, N(%)	48 (87.3)	59 (85.5)	75 (92.6)
Number of bleeds	160	345	505
Haemostatic response, N(%)			
N	160 (100.0)	345 (100.0)	505 (100.0)
Excellent	69 (43.1)	227 (65.8)	296 (58.6)
Good	62 (38.8)	92 (26.7)	154 (30.5)
Moderate	18 (11.3)	18 (5.2)	36 (7.1)
None	3 (1.9)	6 (1.7)	9 (1.8)
Missing	8 (5.0)	2 (0.6)	10 (2.0)
Success/failure, N(%)			
N	152 (100.0)	343 (100.0)	495 (100.0)
Success	131 (86.2)	319 (93.0)	450 (90.9)
Failure	21 (13.8)	24 (7.0)	45 (9.1)
Success/failure, N(%) (incl. missing as failure)			
N	160 (100.0)	345 (100.0)	505 (100.0)
Success	131 (81.9)	319 (92.5)	450 (89.1)
Failure	29 (18.1)	26 (7.5)	55 (10.9)
Success rate*			
Rate	87.1	92.5	90.0
95% CI	77.7 ; 92.9	88.5 ; 95.2	85.4 ; 93.2
Success rate (incl. missing as failure)*			
Rate	81.8	91.9	87.6
95% CI	72.3 ; 88.6	87.5 ; 94.8	82.7 ; 91.3

Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns, with data from the relevant period.
A successfully treated bleed is a bleeding episode where the treatment response was excellent or good.
Bleeds treated only with by-passing agents are excluded.
* Rate estimate and 95% CI obtained from a binomial model, with subject random effects.

Table 40: Haemostatic response for surgery - main + extension - full analysis set

	Minor surgery	Major surgery	Total
Number of patients	25	3	26
Number of surgeries	30	4	34
Haemostatic response, N(%)			
N	30 (100.0)	4 (100.0)	34 (100.0)
Excellent	18 (60.0)	2 (50.0)	20 (58.8)
Good	7 (23.3)	2 (50.0)	9 (26.5)
Moderate	1 (3.3)	0 (0.0)	1 (2.9)
None	2 (6.7)	0 (0.0)	2 (5.9)
Missing	2 (6.7)	0 (0.0)	2 (5.9)
Success/failure, N(%)			
N	28 (100.0)	4 (100.0)	32 (100.0)
Success	25 (89.3)	4 (100.0)	29 (90.6)
Failure	3 (10.7)	0 (0.0)	3 (9.4)
Success/failure, N(%) incl. missing as failure			
N	30 (100.0)	4 (100.0)	34 (100.0)
Success	25 (83.3)	4 (100.0)	29 (85.3)
Failure	5 (16.7)	0 (0.0)	5 (14.7)

A successful haemostatic response was where the treatment response was excellent or good.

Table 41: Number of injections and average dose level with N8-GP for prophylaxis – main + extension - full analysis set

	Pre-prophylaxis	Prophylaxis	Total
Number of patients	55	69	81
Total number of prophylaxis doses per patient*			
N	0	69	69
Mean (SD)	- (-)	236.6 (208.2)	236.6 (208.2)
Median	-	177.0	177.0
Min ; Max	- ; -	7.0 ; 792.0	7.0 ; 792.0
Average prophylaxis dose** (IU/kg)			
N	0	15762	15762
Mean (SD)	- (-)	68.9 (7.6)	68.9 (7.6)
Median	-	69.0	69.0
Min ; Max	- ; -	0.3 ; 274.0	0.3 ; 274.0

Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns, with data from the relevant period.
* N is the number of patients.
** N is the number of doses.
SD: standard deviation.

Table 42: Number of injections and average dose level of N8-GP per bleed - main + extension - full analysis set

	Pre-prophylaxis	Prophylaxis	Total
Number of patients	55	69	81
Number of patients with bleeds, N(%)	48 (87.3)	59 (85.5)	75 (92.6)
Number of bleeds	160	345	505
Number of injections to treat the bleed*, N (%)			
N	160 (100.0)	345 (100.0)	505 (100.0)
1 injection	119 (74.4)	286 (82.9)	405 (80.2)
2 injections	19 (11.9)	36 (10.4)	55 (10.9)
3 injections	12 (7.5)	14 (4.1)	26 (5.1)
4 injections	4 (2.5)	1 (0.3)	5 (1.0)
5 injections	-	3 (0.9)	3 (0.6)
6 injections	2 (1.3)	1 (0.3)	3 (0.6)
7 injections	1 (0.6)	1 (0.3)	2 (0.4)
8 injections	1 (0.6)	-	1 (0.2)
9 injections	-	1 (0.3)	1 (0.2)
10 injections	-	1 (0.3)	1 (0.2)
11 injections	1 (0.6)	1 (0.3)	2 (0.4)
12 injections	1 (0.6)	-	1 (0.2)
N	160	345	505
Mean (SD)	1.6 (1.6)	1.3 (1.1)	1.4 (1.3)
Median	1.0	1.0	1.0
Min ; Max	1.0 ; 12.0	1.0 ; 11.0	1.0 ; 12.0
Average dose for treatment of bleed* (IU/kg/bleed)			
N	160	345	505
Mean (SD)	112.9 (113.4)	92.1 (71.7)	98.6 (87.5)
Median	73.5	70.9	71.4
Min ; Max	35.7 ; 915.3	25.5 ; 852.0	25.5 ; 915.3

Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns, with data from the relevant period.
Only bleeds treated with N8-GP pegol are included.
* N is the number of bleeds.
SD: standard deviation.

Table 43: Consumption of N8-GP - main + extension - full analysis set

	Pre-prophylaxis	Prophylaxis	Total
Number of patients	55	69	81
Consumption used for treatment* per year per patient** (IU/kg/year)			
N	50	69	76
Mean (SD)	2108.6 (2697.6)	5394.9 (1887.9)	4525.7 (2129.2)
Median	1490.6	5155.1	4027.0
Min ; Max	87.4 ; 17904.4	2017.2 ; 9456.7	450.9 ; 9083.4

Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns, with data from the relevant period.
* Consumption used for treatment includes all doses given. Yearly consumption is only calculated for patients with a exposure time of at least 30 days.
** N is the number of patients.
SD: standard deviation.

Ancillary analyses

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 44: Summary of Efficacy for trial 3885

Title: A Multinational, Open-Label, Non-Controlled Trial on Safety, Efficacy and Pharmacokinetics of NNC 0129-0000-1003 in Previously Treated Paediatric Patients with Severe Haemophilia A			
Study identifier	NN7088-3885		
Design	Open-labelled and non-controlled trial to assess safety including immunogenicity, efficacy and pharmacokinetics of N8-GP in prophylaxis and treatment of bleeding episodes in previously treated paediatric patients with severe haemophilia A		
	Duration of main phase: Duration of Extension phase:		20 February 2013 - 15 September 2014 28 September 2018
Hypothesis	Primary objective: • To evaluate immunogenicity of N8-GP Secondary objectives: • To evaluate safety other than immunogenicity of N8-GP • To evaluate efficacy of N8-GP in prophylaxis and treatment of bleeding episodes • To evaluate pharmacokinetic properties of N8-GP and compare to previous FVIII product (only pharmacokinetic [PK] assessments) • To support a population-based PK model for N8-GP (only PK assessments) • To evaluate patient reported outcomes (PRO)		
Treatments groups	Prophylaxis		60 (50-75 to allow for full ml dosing) IU/Kg twice weekly; 68 patients (34 and 34 patients 0-5 and 6-11 years old at enrolment respectively)
Endpoints and definitions	Primary endpoint	Safety	Number of Participants With Inhibitory Antibodies Against Coagulation Factor VIII (FVIII) ⩾0.6 Bethesda Units during the main phase

	Secondary endpoint	Safety	Incidence of inhibitory antibodies against FVIII ⩾0.6 BU during the compiled main and extension phase of the trial Frequency of AEs including SAEs reported during the trial period
	Secondary endpoint	Efficacy	Haemostatic effect of N8-GP when used for treatment of bleeding episodes and assessed as: excellent, good, moderate or none Number of bleeding episodes during prophylactic treatment with N8-GP (annualised bleeding rate) Consumption of N8-GP per bleeding episode (number of injections and IU/kg) Consumption of N8-GP during prophylaxis (number of injections and IU/kg per month and year) Changes in PRO scores from baseline to the end of treatment in main phase and during the extension phase PK endpoints: Incremental recovery at 30 minutes, Area under the curve, Terminal half-life, Clearance
Database lock	15 November 2018		

Results and Analysis

Analysis description	**Efficacy Analysis**			
Analysis population and time point description	All trial patients allocated to treatment, for which at least one of the PK or efficacy endpoints was assessed, were included in the FAS. The FAS trial patients were analysed according to their received treatment.			
Descriptive statistics and estimate variability	Age group	0-5	6-11	Total
	Number of subject	34	34	68
	Haemostatic response in treatment of bleeds (95% CI)	88.3 (76.3 ; 94.6)	80.1 (71.5 ; 86.6)	83.7 (77.0 ; 88.8)
	Poisson estimate of **ABR** 95% CI	1.09 (0.54; 2.19)	1.33 (0.74; 2.39)	1.22 (0.79; 1.87)
	Consumption per bleeding episode (IU/Kg/year) – mean (SD), median, min, max	6778.6 (1039); 6812.0; 3121.8 ; 9131.3	6760.4 (181.8); 6767.9; 6265.3 ; 7168.3	6769.5 (740.1); 6784.6; 3121.8 ; 9131.3
	Prophylaxis dose - mean (SD), median, min, max	65.4 (7.5); 66.5; 11.0 ; 258.1	64.1 (5.3); 64.0; 8.3 ; 114.6	64.7 (6.4); 65.1; 8.3 ; 258.1

	Average dose for treatment of bleed from start to stop of bleed (IU/kg/bleed) - mean (SD), median, min, max	102.8 (81.0); 68.8; 44.9 ; 564.9	91.0 (58.3); 66.9; 29.7 ; 344.8	94.9 (66.7); 68.2; 29.7 ; 564.9
	Average dose for treatment of bleed using <=2 doses+ (IU/kg/bleed) - mean (SD), median, min, max	78.4 (26.8); 68.3; 44.9 ; 145.5	73.6 (25.4); 65.4; 29.7 ; 146.8	75.1 (25.9); 66.7; 29.7 ; 146.8

Table 45: Summary of Efficacy for trial 4410

Title: Safety and Efficacy of turoctocog alfa pegol (N8-GP) in Prophylaxis and Treatment of Bleeds in Previously N8-GP Treated Patients with Severe Haemophilia A			
Study identifier	NN7088-4410		
Design	Multi-centre, multi-national, open-label, non-randomised trial evaluating safety and efficacy of turoctocog alfa pegol during prophylaxis treatment and treatment of bleeds.		
	Duration of main phase:		30 April 2018- 03 December 2020
Hypothesis	Primary objective • To investigate the safety of N8-GP during continuous use for prevention and treatment of bleeding episodes of previously N8-GP treated severe haemophilia A patients during the 104 weeks trial period. Secondary objectives • To investigate the following in severe haemophilia A patients previously treated with N8-GP during the 104 weeks trial period. - Development of FVIII inhibitors - Efficacy of N8-GP prophylaxis - Haemostatic efficacy of N8-GP when used for treatment of bleeds - Joint health status - Haemostatic efficacy during major surgical interventions - Treatment satisfaction in patients receiving N8-GP prophylaxis - To evaluate the health economic impact of N8-GP treatment		
Treatments groups	Prophylaxis		60 IU/kg BW twice weekly
Endpoints and definitions	Primary endpoint	Safety	Number of adverse events reported
	Secondary endpoint	Safety	Incidence of FVIII inhibitors ≥0.6 BU

	Secondary endpoint	Efficacy	Number of bleeding episodes on prophylaxis Number of spontaneous bleeding episodes on prophylaxis Haemostatic effect of N8-GP when used for treatment of bleeding episodes assessed as: Excellent, Good, Moderate, or None Number of N8-GP injections required per bleeding episode Pre-dose FVIII activity levels on N8-GP prophylaxis Change in joint health status from start to end of trial Haemostatic response during major surgical interventions Change from baseline till end of trial in treatment satisfaction (Hemo-SAT)
Database lock	11 February 2021		
Results and Analysis			
Analysis description	**Efficacy Analysis**		
Analysis population and time point description	All trial patients allocated to treatment, for which at least one of the PK or efficacy endpoints was assessed, were included in the FAS. The FAS trial patients were analysed according to their received treatment.		
Descriptive statistics and estimate variability	Age group	0-11	
	Number of subjects	34	
	Poisson estimate of **ABR** (95% CI)	0.86 (0.38; 1.97)	
	Haemostatic response success rates 95% CI	100% treatment success	

Table 46: Summary of Efficacy for trial 3908

Title: An open-label single-arm multicentre non-controlled phase 3a trial investigating safety and efficacy of N8-GP in prophylaxis and treatment of bleeding episodes in previously untreated paediatric patients with severe haemophilia A		
Study identifier	NN7088-3908	
Design	Open-label single-arm multicentre non-controlled phase 3a trial investigating safety and efficacy of N8-GP in prophylaxis and treatment of bleeding episodes in previously untreated paediatric patients with severe haemophilia A	
	Duration of main phase:	26 June 2014 – primary completion: 11 November 2021

Hypothesis	Primary objective • To evaluate immunogenicity of N8-GP in previously untreated patients (PUPs) with severe haemophilia A Secondary objectives • To evaluate safety other than immunogenicity of N8-GP in PUPs with severe haemophilia A • To evaluate efficacy of N8-GP in PUPs with severe haemophilia A in: - long-term prophylaxis treatment (bleeding preventive effect) - the treatment of bleeding episodes		
Treatments groups	Pre-prophylaxis		60 (50-75 to allow for full ml dosing) IU/Kg, >1 week between doses: 55 patients
	Prophylaxis		Main phase: 60 IU/Kg (50-75IU/kg) , every 3rd day, twice weekly or every 7th day (± 1 day) Extension phase: 60 IU/Kg (50-75IU/kg) , every 3rd day, twice weekly or every 4th day, every 5th day, every 6th day or every 7th day (± 1 day) 69 patients
Endpoints and definitions	Primary endpoint	Safety	Incidence of FVIII inhibitors
	Secondary endpoint	Efficacy	Details of bleeds Annualised bleeding rate (ABR) during pre-prophylaxis and prophylaxis with N8-GP Haemostatic effect of N8-GP when used for treatment of bleeding episodes Haemostatic effect of N8-GP during surgery Consumption of N8-GP for prophylaxis Consumption of N8-GP for treatment of bleeds Total consumption of N8-GP per patient (prevention and treatment of bleeding episodes) Clinical effect of ITI treatment
	Secondary endpoint	Pharmaco-kinetics	FVIII activity; Incremental recovery (30 min post-dose);
Database lock	Interim1: Data cut-off 01 October 2019 Interim 2: Data cut-off 31 August 2020 Final CTR: 10 January 2022 (Database lock)		

Results and Analysis

Analysis description	**Efficacy Analysis**			
Analysis population and time point description	All trial patients allocated to treatment, for which at least one of the PK or efficacy endpoints was assessed, were included in the FAS. The FAS trial patients were analysed according to their received treatment.			
Descriptive statistics and estimate variability	Age group	Pre-prophylaxis	Prophylaxis	Total
	Number of subject	55	69	81
	Poisson estimate of **ABR** 95% CI		2.12; 1.34; 3.37	2.12; 1.34; 3.37

	Haemostatic response – treatment success rate 95% CI	87.1%; 77.7%; 92.9%	92.5%; 88.5% ; 95.2%	90.9%; 85.4% ; 93.2%
	Haemostatic response for surgery – treatment success rate	89.3%	100%	90.6%
	Average prophylaxis dose mean (SD); median; min; max		236.6 (208.2); 177.0; 7.0 ; 792.0	236.6 (208.2); 177.0; 7.0 ; 792.0
	Average dose for treatment of bleed (IU/kg/bleed) - mean (SD); median; min; max	112.9 (113.4); 73.5; 35.7 ; 915.3	92.1 (71.7); 70.9; 25.5 ; 852.0	98.6 (87.5); 71.4; 25.5 ; 915.3
	Total consumption per year per patient - mean (SD); median; min; max	2108.6 (2697.6); 1490.6; 87.4 ; 17904.4	5394.9 (1887.9); 5155.1; 2017.2 ; 9456.7	4525.7 (2129.2); 4027.0; 450.9 ; 9083.4

Supportive study(ies)

Trial NN7088-3859

Study 3859 was ongoing but considered as main study during the initial marketing authorisation application and was assessed accordingly during initial MAA procedure. For a detailed presentation of the study design and results presented for the initial MAA please refer to the respective EPAR. Here results of the now completed study will be briefly presented.

Table 47: N8-GP exposure - full analysis set

	N8-GP 50 IU/kg prophylaxis Q4D	N8-GP 75 IU/kg prophylaxis Q7D	N8-GP 20-75 IU/kg on-demand	Total
Number of patients*	177	61	12	186
Total time on regimen in trial (years)	613.36	134.86	37.19	785.41
Total number of doses per patient				
N	177	61	12	186
Mean (SD)	326.9 (208)	119.3 (92.9)	136.8 (149)	359.0 (196)
Median	363.0	118.0	78.5	413.5
Min ; Max	1 ; 713	4 ; 250	20 ; 557	1 ; 713
Total time on regimen in trial per patient (days)				
N	177	61	12	186
Mean (SD)	1266 (790)	807.5 (637)	1132 (802)	1542 (772)
Median	1479	798.0	786.0	1974
Min ; Max	5 ; 2269	18 ; 1689	126 ; 2318	5 ; 2397
Total number of exposure days per patient				
N	177	61	12	186
Mean (SD)	326.1 (207)	118.9 (92.6)	133.3 (145)	357.9 (195)
Median	363.0	117.0	78.5	413.0
Min ; Max	1 ; 697	4 ; 250	20 ; 542	1 ; 697
Total number of prophylaxis doses per patient				
N	177	61	12	186
Mean (SD)	315.9 (200)	114.8 (91.2)	4.8 (5.8)	338.6 (195)
Median	362.0	114.0	2.0	393.5
Min ; Max	1 ; 616	3 ; 240	2 ; 21	1 ; 616
Total number of doses used for treatment of bleed per patient				
N	128	53	12	152
Mean (SD)	14.1 (20.7)	4.9 (4.3)	128.8 (148)	23.7 (54.3)
Median	6.0	3.0	73.5	8.5
Min ; Max	1 ; 106	1 ; 18	15 ; 553	1 ; 553
Total number of doses used for minor surgery per patient				
N	42	5	6	51
Mean (SD)	3.4 (4.3)	2.8 (4.0)	6.3 (6.5)	3.8 (4.7)
Median	2.0	1.0	4.5	2.0
Min ; Max	1 ; 26	1 ; 10	2 ; 19	1 ; 26

* Several patients changed treatment regimen during the trial. Therefore a patient may be included in more than one treatment arm, but only counted once in the total.
Total number of exposure days in trial is calculated as number of days with doses (excluding surgery).
Day is only counted once if more than one dose is taken during the day.

Table 48: Annualised bleeding rate - full analysis set

	N8-GP 50 IU/kg prophylaxis Q4D	N8-GP 75 IU/kg prophylaxis Q7D	N8-GP 20-75 IU/kg on-demand
Number of patients	177	61	12
Number of patients with bleeds, N (%)	126 (71.2)	53 (86.9)	12 (100.0)
Number of patients with LOCF	41	38	3
Number of observed bleeds	1312	176	1270
Number of bleeds using imputation*	1552	1117	1347
Number of patients with less than 1 month exposure	6	2	0
Bleeds per patient (min ; max)*	0 ; 81	0 ; 115	10 ; 476
Mean treatment period (years)**	3.73	4.17	3.53
Annualised bleeding rate			
Individual ABRs			
N	177	61	12
Mean (SD)	2.74 (4.85)	4.41 (6.07)	32.78 (19.35)
Median	0.99	1.95	31.03
Interquartile range	0.00 ; 2.68	0.43 ; 6.52	22.72 ; 39.82
Min ; Max	0.00 ; 25.19	0.00 ; 24.18	4.62 ; 75.00
Poisson estimate of ABR	2.35	4.39	-
95% CI	1.87 ; 2.95	3.09 ; 6.24	-
P-value+	<0.001	<0.001	-
Negative binomial estimate of ABR++	2.64	4.41	-
95% CI	2.11 ; 3.30	3.10 ; 6.26	-
P-value+	<0.001	<0.001	-

ABR: annualised bleeding rate, CI: confidence interval, LOCF: last observation carried forward, SD: standard deviation.
The analysis is based on a Poisson regression model allowing for over-dispersion. For patients withdrawing prematurely, the log planned treatment duration is used as offset; for completers, the log actual treatment duration is used.
Total column not present, since total has no meaningful interpretation in this table.
* Imputation: For patients withdrawing prematurely, the number of bleeding episodes is imputed up according to the planned treatment duration. For patients with <1 month of exposure, the annual bleeding rate is imputed as 24 episodes per year for the missing period.
** For patients withdrawing prematurely, the planned treatment duration is used; for completers, the actual treatment duration is used.
+ P-values are from the 1-sided test of the null hypothesis that the ABR is at least 8.5 evaluated at the 2.5% level.
++ Additional sensitivity analysis based on a negative binomial model.

Table 49: Haemostatic response - full analysis set

	N8-GP 50 IU/kg prophylaxis Q4D	N8-GP 75 IU/kg prophylaxis Q7D	N8-GP 20-75 IU/kg on-demand	Total
Number of patients*	177	61	12	186
Number of patients with bleeds**, N(%)	126 (71.2)	53 (86.9)	12 (100.0)	152 (81.7)
Number of bleeds**	1312	176	1270	2758
Haemostatic response, N(%)				
N	1312 (100.0)	176 (100.0)	1270 (100.0)	2758 (100.0)
Excellent	600 (45.7)	75 (42.6)	859 (67.6)	1534 (55.6)
Good	532 (40.5)	65 (36.9)	339 (26.7)	936 (33.9)
Moderate	153 (11.7)	29 (16.5)	71 (5.6)	253 (9.2)
None	6 (0.5)	2 (1.1)	1 (0.1)	9 (0.3)
Missing	21 (1.6)	5 (2.8)	0 (0.0)	26 (0.9)
Success/failure (incl. missing as failure), N(%)				
N	1312 (100.0)	176 (100.0)	1270 (100.0)	2758 (100.0)
Success	1132 (86.3)	140 (79.5)	1198 (94.3)	2470 (89.6)
Failure	180 (13.7)	36 (20.5)	72 (5.7)	288 (10.4)
Success/failure, N(%)				
N	1291 (100.0)	171 (100.0)	1270 (100.0)	2732 (100.0)
Success	1132 (87.7)	140 (81.9)	1198 (94.3)	2470 (90.4)
Failure	159 (12.3)	31 (18.1)	72 (5.7)	262 (9.6)
Success rate (incl. missing as failure)				
Rate (%)	83.7	80.0	88.6	83.2
95% CI	79.8 ; 87.0	71.8 ; 86.3	81.1 ; 93.4	79.7 ; 86.2
p-value***	<.001	<.001	<.001	<.001
Success rate				
Rate (%)	85.4	82.7	88.6	84.8
95% CI	81.9 ; 88.3	74.9 ; 88.4	81.1 ; 93.4	81.7 ; 87.6
p-value***	<.001	<.001	<.001	<.001

Analysed using logistic regression accounting for repeated measures within subject assuming compound symmetry working correlation.
* Several patients changed treatment regimen during the trial. Therefore a patient may be included in more than one treatment arm, but only counted once in the total.
** Only bleeds treated with N8-GP are included
*** p-value is from the 1-sided test of the null hypothesis that the success rate is <= 65% at the 2.5% level.

Table 50: Number of injections per bleed - full analysis set

	N8-GP 50 U/kg prophylaxis Q4D	N8-GP 75 U/kg prophylaxis Q7D	N8-GP 20-75 U/kg on-demand	Total
Number of patients*	177	61	12	186
Number of patients with bleeds	126	53	12	152
Number of bleeds	1312	176	1270	2758
Number of injections to treat the bleed**, N (%)				
N	1312 (100.0)	176 (100.0)	1270 (100.0)	2758 (100.0)
1 injection	988 (75.3)	131 (74.4)	1113 (87.6)	2232 (80.9)
2 injections	238 (18.1)	28 (15.9)	119 (9.4)	385 (14.0)
3 injections	42 (3.2)	6 (3.4)	19 (1.5)	67 (2.4)
4 injections	23 (1.8)	6 (3.4)	4 (0.3)	33 (1.2)
5 injections	10 (0.8)	2 (1.1)	6 (0.5)	18 (0.7)
6 injections	4 (0.3)	-	1 (0.1)	5 (0.2)
7 injections	2 (0.2)	2 (1.1)	-	4 (0.1)
8 injections	1 (0.1)	-	1 (0.1)	2 (0.1)
9 injections	3 (0.2)	-	1 (0.1)	4 (0.1)
10 injections	-	1 (0.6)	-	1 (0.0)
11 injections	-	-	1 (0.1)	1 (0.0)
12 injections	-	-	3 (0.2)	3 (0.1)
13 injections	-	-	1 (0.1)	1 (0.0)
18 injections	-	-	1 (0.1)	1 (0.0)
24 injections	1 (0.1)	-	-	1 (0.0)
N	1312	176	1270	2758
Mean (SD)	1.4 (1.1)	1.5 (1.2)	1.2 (1.0)	1.3 (1.1)
Median	1.0	1.0	1.0	1.0
Min ; Max	1 ; 24	1 ; 10	1 ; 18	1 ; 24

* Several patients changed treatment regimen during the trial. Therefore a patient may be included in more than one treatment arm, but only counted once in the total.
**N is number of bleeds

Table 51: Actual consumption - full analysis set

	N8-GP 50 IU/kg prophylaxis Q4D	N8-GP 75 IU/kg prophylaxis Q7D	N8-GP 20-75 IU/kg on-demand	Total
Number of patients*	177	61	12	186
Consumption used for treatment** per year per patient*** (IU/kg/year)				
N	177	61	12	186
Mean (SD)	4829 (628.8)	4242 (394.5)	1562 (830.3)	4554 (971.8)
Median	4808	4108	1528	4743
Min ; Max	416 ; 6799	3827 ; 6473	388 ; 3278	388 ; 6799
Consumption used for treatment** per month per patient*** (IU/kg/month)				
N	177	61	12	186
Mean (SD)	402.4 (52.4)	353.5 (32.9)	130.2 (69.2)	379.5 (81.0)
Median	400.7	342.3	127.4	395.3
Min ; Max	35 ; 567	319 ; 539	32 ; 273	32 ; 567
Consumption used for prophylaxis per year per patient*** (IU/kg/year)				
N	177	61	12	186
Mean (SD)	4674 (550.0)	3938 (270.3)	94.3 (112.4)	4328 (1123.7)
Median	4744	4001	72.3	4664
Min ; Max	416 ; 5636	3099 ; 4855	16 ; 436	16 ; 5636
Consumption used for treatment (excl surg doses)+ per year per patient*** (IU/kg/year)				
N	177	61	12	186
Mean (SD)	4818 (626.8)	4238 (395.3)	1504 (781.8)	4543 (973.8)
Median	4804	4108	1476	4740
Min ; Max	416 ; 6799	3827 ; 6473	388 ; 2908	388 ; 6799
Average prophylaxis dose++ (IU/kg)				
N	55896	6996	58	62950
Mean (SD)	52.2 (1.5)	77.1 (3.2)	37.5 (13.0)	55.0 (8.0)
Median	52.2	77.2	28.4	52.3
Min ; Max	7 ; 106	5 ; 112	23 ; 56	5 ; 112

*Several patients changed treatment regimen during the trial. Therefore a patient may be included in more than one treatment arm, but only counted once in the total.
**Consumption used for treatment incl all doses given (prophylaxis, treatment of bleeds, on-demand, minor surgery, and PK) excluding doses during major surgery.
***N is number of patients
+Doses for minor surgery have been excluded
++N is number of doses

Trial NN7088-3860

Study 3860 was ongoing and considered as supportive study during the initial marketing authorisation application and was assessed accordingly during initial MAA. For a detailed presentation of the study design and results presented for licensure please refer to the respective EPAR. Here results of the now completed study will be briefly presented.

Table 52: Surgery details

	Total
Number of patients	36
Number of patients undergoing surgery	35
Number of surgeries	49
Cause of surgery	
N (%)	49 (100.0)
Elective surgery	46 (93.9)
Emergency surgery	3 (6.1)
Location of surgery	
N (%)	49 (100.0)
Abdomen	2 (4.1)
Abdominal	1 (2.0)
Bilateral thumbs	1 (2.0)
Both ankles	1 (2.0)
Chest	1 (2.0)
Knee right	1 (2.0)
Left and right knee	1 (2.0)
Left ankle	7 (14.3)
Left elbow	3 (6.1)
Left hip	1 (2.0)
Left knee	6 (12.2)
Left shoulder	1 (2.0)
Penis	1 (2.0)
Right ankle	4 (8.2)
Right elbow	2 (4.1)
Right femoral neck	1 (2.0)
Right hip	2 (4.1)
Right knee	11 (22.4)
Right leg	1 (2.0)
Right talar	1 (2.0)
Time of surgery start	
N (%)	49 (100.0)
From 7 a.m to 11 a.m.	21 (42.9)
From 11 a.m to 3 p.m.	23 (46.9)
From 3 p.m to 7 p.m.	5 (10.2)
Duration of surgery (hours)	
N	48
Mean (SD)	1.8 (1.0)
Median	1.8
Min ; Max	0.2 ; 5.8

SD: standard deviation.
During surgery: time from knife to skin until last stitch.
Duration of surgery summarised only when time information is available.

Table 53: Haemostatic effect of N8-GP during surgery - full analysis set

	Total
Number of patients	36
Number of patients undergoing surgery	35
Number of surgeries	49
Haemostatic response	
N (%)	49 (100.0)
Excellent	25 (51.0)
Good	22 (44.9)
Moderate	2 (4.1)
None	0 (0.0)

Success: excellent or good haemostatic response.
Failure: moderate or none haemostatic response.
During surgery: time from knife to skin until last stitch.

Table 54: Estimated blood loss during surgery - full analysis set

	Total
Number of patients	36
Number of patients undergoing surgery	35
Number of surgeries	49
Estimated blood loss (mL)	
N	45
Mean (SD)	322.6 (745.0)
Median	75.0
Min ; Max	0.0 ; 4520.0

SD: standard deviation.
N: number of surgeries with reported blood loss.
Anticipated blood loss is from an evaluation done prior to surgery. Estimated blood loss is from an evaluation done post-surgery.

Table 55: N8-GP consumption on the day of surgery (day 0) – full analysis set

		Consumption (IU/kg)		
	N	Mean	Median	Min ; Max
Pre-surgery (day 0)	49	55.7	51.2	27.2 ; 86.2
During surgery (day 0)[a, b]	1	20.7	20.7	20.7 ; 20.7
Post-surgery (day 0)[a]	31	30.7	26.2	10.1 ; 58.8
Post-surgery (day 0)	49	19.4	20.5	0.0 ; 58.8
On day of surgery (day 0)	49	75.5	74.5	27.2 ; 136.2

[a] Excluding patients who did not get any dose
[b] During surgery is defined from 'knife to skin' until 'last stitch'.
N: number of surgeries.

Trial NN7088-4595

Trial NN7088-4595 was a multi-centre, open-label trial evaluating efficacy, safety and pharmacokinetics of turoctocog alfa pegol (N8-GP) when used for treatment and prophylaxis of bleeding episodes in previously treated Chinese patients with haemophilia A. The trial was conducted at 8 sites in China mainland.

Methodology

This trial design was overall similar to the design of the completed global, pivotal pathfinderTM2 trial in adolescent and adult previously treated patients with severe haemophilia A (trial NN7088-3859). Thirty-six (36) Chinese PTPs with severe haemophilia A, aged ≥12 years and with ≥150 exposure days (EDs) to other FVIII product(s), received prophylaxis with 50 IU/kg N8-GP every 4 days (with the possibility of switching to twice-weekly dosing during the treatment period at the discretion of the investigator). Bleeding episodes were treated with bolus injection(s) of 20-75 IU/kg N8-GP.

A total of 36 Chinese patients (adolescents/adults) with haemophilia A were planned to be offered to participate in this trial. Of these 36 patients, at least 30 patients were expected to complete the trial with ≥50 EDs to N8-GP (including treatment of bleeding episodes) and ≥6 months (≥28 weeks) of prophylaxis. A total of 36 patients were enrolled and exposed to N8-GP during the trial. The full analysis and safety analysis sets consisted of all 36 patients enrolled into the trial. All 36 patients completed the trial. There were no withdrawals/discontinuation during the trial.

Summary of results of the supportive studies

Demographics and other baseline characteristics

The trial population consisted of 36 Chinese male patients with severe haemophilia A (FVIII activity <1%). At baseline, the mean (standard deviation [SD]) age of patients was 23.3 (10.4) years. The minimum patient age was 12 years and the maximum patient age was 54 years in the trial. Of total 36 patients, 13 patients belonged to 12-17 years and 23 patients belonged to ≥18 years. All patients were previously treated, with a history of at least 150 EDs to other FVIII products and no history of inhibitors. Before entry to the trial, 18 (50.0%) patients received regular prophylactic treatment; 17 (47.2%) patients received both prophylactic and on-demand treatment and 1 (2.8%) patient received on-demand treatment within the last 12 months.

Efficacy and pharmacokinetic results

- Prophylactic treatment with 50 IU/kg N8-GP every 4 days was effective for prevention of bleeds. Twenty five (25) of 36 patients (69.4%) reported zero bleeds during the trial. The estimated mean ABR was 2.55 (95% CI: 1.24; 5.23) and median ABR (IQR) was 0.00 (0.00; 1.83).
- N8-GP was successful in treatment of bleeds with a haemostatic success rate of 94.8% (95%CI: 73.2%; 99.2%).
- Majority of bleeds (49 of 52 bleeds) were treated with ≤2 injections.
- The actual mean (SD) consumption of N8-GP for the treatment (including prophylaxis and treatment of bleeds) was 5036.2 (406.8) IU/kg/year and for prophylaxis was 4886.7 (239.9) IU/kg/year. The mean consumption was similar in adolescents and adults.
- The mean (SD) dose of N8-GP used for treatment of bleeds was 61.0 (22.1) IU/kg/bleed and the mean (SD) N8-GP dose used during prophylaxis was 52.5 (1.0) IU/kg.
- The FVIII activity mean trough level was 0.033 (95% CI: 0.026; 0.043) IU/mL and the mean recovery 30 minutes after administration was 1.261 (95% CI: 1.169; 1.360) IU/mL.
- At the first PK session, t½ was 19.9 hours and the incremental recovery at 30 minutes was 0.02 (IU/mL)/(IU/kg).
- The PK parameter values at the second PK (steady state) session were similar.

2.4.2. Discussion on clinical efficacy

Assessment of paediatric data on clinical efficacy

The MAH submitted long term treatment data from three non-controlled open-label studies investigating Esperoct in paediatric subjects with severe Haemophilia A. Trial 3885 followed 68 PTPs (0-11 years) of which 58 subjects continued to long term study 4410. In trial 3908, Esperoct was investigated in 81 PUPs (<7 years). The recommended dose in all paediatric trials for prophylaxis was 60 (50-75) IU/kg, whereas the dose in subjects >12 years is 50 IU/kg.

NN7088-3885 – previously treated paediatric subjects

Design and conduct

Available efficacy data in PTPs from trial 3885 were previously discussed in the scope of the initial licensure of Esperoct. Nonclinical safety data were indicating a potentially increased risk in the paediatric

population in relation to PEG, which hindered licensure for that patient population at that time (see also safety section). With the submission at hand, efficacy data on a longer treatment duration are provided, as an extension of the initially submitted study report. Data are being discussed from both, the main phase and the completed extension phase.

68 patients with severe haemophilia A from ages 0-11 years were included in this study (34 older children and 34 younger children), 63 of which entered the extension period. During the main phase, 5 subjects withdrew from the study, and during the extension phase 1 subject withdrew from the study, which 61 subjects completed. All patients reported efficacy data were part of the full analysis set. Guideline requirements that the clinical study in children 0-12 should be initiated only after 50 EDs are available in patients >12 years of age and that the investigation should begin with PK followed by investigation of efficacy and safety for at least 50 EDs in 50 children were met. Prior to trial entry younger children had a mean of 206.9 EDs, and older children a mean 809.9 EDs with a previous FVIII product. The study design and study conduct appear in line with requirements outlined in the respective guideline, with an even longer observation period. As per guidance efficacy and safety should be followed in 50 children (0 to <12y) for 50 EDs. Study 3885 followed 68 patients <12 years (n=34, 0-5 years old and n=34, 6-11 years old) for a mean/median duration of 472.6/504.5 EDs per patient, which is considered sufficiently long to conclude on long-term efficacy.

Efficacy data in paediatric PTPs

The evaluation of immunogenicity was the primary aim of this study. The focus on immunogenicity in paediatric trials as well as the reported efficacy endpoints (e.g. bleeding rate, haemostatic response and Factor FVIII consumption) are acknowledged and well in line with data provided for other Factor FVIII products. Regarding the primary objective, no confirmed FVIII inhibitors developed during the trial, which is acknowledged. In younger children a total of 108 bleeds occurred in 26 (76.5%) patients and the mean individual ABR was 3.05 (SD: 9.74; min: 0, max: 45.66) with a Poisson estimate concluded on an ABR of 1.09 (95%CI: 0.54; 2.19; negative binominal estimate: 2.93 with 95%CI: 1.74; 4.92). In older children a total of 222 bleeds occurred in 29 (85.3%) patients and the mean individual ABR was 1.34 (SD: 1.36; min: 0, max: 6.16) with a Poisson estimate concluded on an ABR of 1.33 (95%CI: 0.74; 2.39; negative binominal estimate: 1.34 with 95%CI: 0.84; 2.16). Importantly, data demonstrate sufficient prophylactic bleeding control. The majority of bleeds were of traumatic origin (69.4% and 66.2% in 0-5 and 6-11 years), of mild/moderate severity (98.1% and 99.5%) and the majority of bleeds was located at joints (38.9% and 55% of all bleeds) and the majority of patients had joint bleeds (64.7% across age groups). Of the total 162 joint bleeds that have occurred during the study, 72 were of spontaneous origin (43.9%). Of note, the haemostatic response for joint bleeds was mostly successful (76.6% across age groups). A total of 5 and 8 PTPs are reported with 7 and 10 target joints at baseline for 0-5 and 6-11 year old patients and during trial 3885. During the trial 85.7% and 20% of target joints resolved in younger and older children, respectively. Upon request the MAH clarified that 1 patient (6-11 years old) has developed 2 new target joints during the study. Importantly, both target joints also resolved during the study on continued N8-GP prophylaxis. The haemostatic response was good or excellent in the vast majority of subjects and were controlled with 1-2 injections (88.2% of all bleeds across age groups), resulting in 89.6% and 78.7% of successfully treated bleeding events. Consequently, treatment failure is reported for 10.4% and 21.3% of PTPs 0-5 years old compared to PTPs 6-11years old, indicating a mildly worse bleeding control in older paediatric patients.

The success rate was similar between spontaneous and traumatic bleeds. Two bleeding events per age group were not controlled by Esperoct, but the majority of failed treatments were due to moderate responses (8.3% and 19.8%). Importantly, no rebleed occurred after successful control of a bleeding event. The average dose to treat a bleed was 68.8 and 66.9 IU/kg. All together, data on efficacy indicate a well controlled bleeding risk during the prophylactic treatment with Esperoct in PTPs of 0-5 and 6-11 years. However, the control of breakthrough bleeds appears more reliable in 0-5 year old PTPs compared

to 6-11 year old PTPs based on the higher rate of treatment failures in the elder group (around double compared to the younger group). The IP was administered twice weekly. However, the average prophylactic dose was 65.4 and 64.1 IU/kg, which is around 10% more than the recommended dosing during the study. The dosing recommendation is adjusted to 65 IU/kg accordingly.

It is noted that several of the subjects might have crossed age groups during the trial as they became older in the course of study conduct. Thus, these subjects can be accounted for in different age categories, some might have become adolescent and adult during the trial, or switch form age category 0-5 years to age category 6-11 years. The purpose of this variation is the licensure of treatment with N8-PG for paediatric patients and thus, for efficacy evaluation subjects appear most relevant while ≤12 years of age. The MAH reported data on actual age in the SmPC, which do not indicate any concerning differences to the results reported in the CSR. In total 45 minor surgeries have been conducted during the trial (19 and 26 in 9 and 14 PTPs 0-5 and 6-11 year old) with an average median dose of 76 and 63.8 IU/kg used as additional prophylaxis. Subjects were removed from therapy and assessment in case a major surgery was scheduled for the main phase of the trial, but should have been included in the extension phase. Upon request, the MAH confirmed that no major surgeries were performed during trial 3885 (neither during main, nor during extension phase). The evaluation of the haemostatic response was not required per protocol for minor surgeries. Thus, no data are available. Still, none of the minor surgeries required administration of more than 1 (one) injection of N8-GP.

NN7088-4410 – extension study including PTPs from trial 3885

Design and conduct

Trial 4410 was a long term follow up study, in which patients who had previously completed trial 3859 (PTPs >12 years at baseline) and trial 3885 (PTPs <12 years at baseline) were included. A total of 160 patients were enrolled in this study, of which 58 patients came from trial 3885. Patients were followed for a mean of 179.4 ED per patient. The MAH did not describe patient flow by age at baseline.

Efficacy data in paediatric PTPs

Data was not reported separated by trial of origin, and only separated by age groups for specific results. Therefore, only efficacy data for which age groups were analysed are discussed here. As during trial 3885 paediatric patients followed almost exclusively the twice weekly dosing regimen (only one subject was reported with three times weekly). Number of adverse events reported was the primary endpoint in study 4410, whereas the evaluation of immunogenicity was a secondary endponit of this study. The focus on safety (including immunogenicity) in paediatric trials as well as the reported efficacy endpoints (e.g. bleeding rate, haemostatic response and Factor FVIII consumption) are acknowledged and well in line with data provided for other Factor FVIII products. No FVIII inhibitors >=0.6 BU were identified during the study.

Efficacy, pharmacokinetics and further safety measures were evaluated as secondary objectives. The Poisson estimate of ABR (95% CI) was 0.86 (0.38; 1.97) in subjects 0-11, which was lower than in the other patient groups 12-17 and 18+ years of age and slightly lower compared to results presented in study 3885 (see above). The success rate to treat the 14 bleeds that occured in paediatric patients was 100%. Presented data on efficacy are considered to support the favourable effect of Esperoct,

NN7088-3908 – previously untreated paediatric subjects

Design and conduct

Efficacy in PUPs treated with Esperoct was principally already discussed in detail during a previous type II variation procedure. Please refer to the type II variation procedure EMEA/H/C/004883/II/0013 with final Opinion on February 2023 for a detailed assessment.

In trial 3908 81 PUPs <6 years were enrolled, 55 of which started in the pre-prophylaxis group and 26 in the prophylaxis group. The pre-prophylaxis group consisted of patients who had neither received more than 20 EDs nor turned 24 months of age, while the prophylaxis could begin as early as visit 1 but had to be initiated when the patient exceeded 24 months of age or had received 20 EDs. In total 42 pre-prophylaxis patients switched to the prophylaxis group while 11 withdrew from the study and 2 initiated ITI treatment. 30 patients withdrew from the trial, of which 23 (28.4%) discontinued during the main phase, and 7 (8.6%) during the extension phase. During the main phase reasons for withdrawal were adverse events (n = 7; 8.6%), lack of efficacy (n = 3; 3.7%), loss to follow-up (n = 1; 1.2%), protocol violation (n = 2; 2.5%), withdrawal by parent/guardian (n = 4; 4.9%), withdrawal by subject (n = 2; 2.5%) and 'other' (n = 4; 4.9%). Altogether, 49 PUPs completed the trial. The design and conduct of trial 3908 are considered acceptable to conclude on efficacy of Esperoct in PUPs.

Efficacy data in paediatric PUPs

The primary objective investigated in Trial 3908 was to investigate the immunogenicity of Esperoct in previously untreated patients (PUPs) <6 years with severe haemophilia A with regards to incidence of FVIII inhibitors. In addition to prior data, the MAH provided an addendum to the CSR of study 3908, which includes data for 2 inhibitor patients that have continued immune tolerance treatment after the prior database lock. In total, 26% of subjects included in the trial (21 of 81) have developed Factor VIII inhibitors and 8 of these patients have initiated ITI treatment. Thus, patient numbers are not sufficient to draw any robust conclusions regarding the effect of ITI in PUPs with anti-FVIII inhibitors during the therapy with Esperoct (n=8 PUPs with FVIII-inhibitors started ITI and n=6 had a positive clinical effect). The very common incidence of inhibitors (i.e. frequency ≥1/10 patients) is an expected frequency (as per outcome of the FVIII referral and FVIII Core SmPC) and occurs especially during the first 50 EDs. The choice to assess the development of FVIII inhibitors as primary objective of trial 3908 is supported as anti-drug antibodies are a major concern for PUPs. No concern derives from reported results.

Secondary objectives were safety other than immunogenicity and efficacy in long term prophylaxis treatment and treatment of bleeding episodes. This investigation strategy is consistent with other studies in other FVIII products and is considered acceptable, even though it should be noted that no dedicated studies in PUPs are required per Factor VIII GL. The actual mean (SD) and median prophylaxis dose was 68.9 (7.6) and 69.0 IU/kg, respectively, which, as in PTPs, is higher than the proposed study dose of 60 IU/kg, although not higher than the recommended range of 50-75 IU/kg dose (see SmPC). Patients in the pre-prophylaxis group received a mean/median of 8.1/7.0 doses and had an average treatment period of 0.5 (SD: 0.4) years. In the prophylaxis group, patients received a mean/median of 236.6/177.0 doses and were included for a mean of 2.9 years. On average 4.9 (SD: 4.3) doses were used per pre-prophylaxis patient for the treatment of bleeds compared to a mean 7.9 (SD: 9.3) doses per patient in the prophylaxis group. 163 bleeds occurred (160 treated with Esperoct) in 48 (87.3%) pre-prophylaxis patients, requiring on average 1.6 (SD: 1.6) injections to stop bleeding. In the prophylaxis group, 347 bleeds occurred (345 treated with Esperoct) in 60 (87%) patients and required on average 1.3 (SD: 1.1) doses to treat. The mean individual ABR during prophylaxis was 3.46 (SD: 7.1; min: 0, max: 49.81) and the Poisson estimate concluded on an ABR of 2.12 (95%CI: 1.34; 3.37). Of note, the mean individual ABR in PTPs of the same age group (0-5years) was 3.05 (SD: 9.74; min: 0, max: 45.66) with a Poisson estimate concluded on an ABR of 1.09 (95%CI: 0.54; 2.19). This mildly lower ABR is likely related to the actual age difference between the populations of PUPs (mean age 10.2 month) and PTPs (mean age 3

years). No concerns arise. The majority of bleeds were of traumatic origin (80.69% during prophylaxis and 63.8% during pre-prophylaxis), of mild/moderate severity (97.41% during prophylaxis and 95.71% during pre-prophylaxis) and at the skin (42.07% during prophylaxis and 46.63% during pre-prophylaxis). Severe bleeds were not common in the general population of PUPs (2.59% during prophylaxis and 2.45% during pre-prophylaxis), but 2 severe bleeds occurred at the CNS level. All bleeds at the CNS level were of traumatic origin and 5 of 7 bleeds were treated with successful haemostatic response. For details of CNS bleeds, please refer to the clinical safety section. The haemostatic response for the treatment of bleeds was mostly rated as success (93% during prophylaxis and 86.2% during pre-prophylaxis) with a high proportion of excellent responses (65.8% during prophylaxis and 43.1% during pre-prophylaxis) and most bleeds were treated with a single injection (82.9% during prophylaxis and 74.4% during pre-prophylaxis). The positive success rate was also observed in the haemostatic response for surgery, with success in all major surgeries (n=4 in 3 patients) and in 86.3% of minor surgeries (n=30 in 25 patients). Of note, bleeding in two minor surgeries was not controlled by Esperoct and a median of 3 doses were used during surgery. The average dose to treat a bleed was 70.9 IU/kg (in the prophylactic group, 73.5 IU/kg/bleed in the pre-prohylactic group) and the average prophylactic dose was 68.9 IU/kg, which is around 10-20% more than the recommended dosing during the study. Dosing recommendations in the PI were adjusted to 65 IU/kg (50-75 IU/kg). In conclusion, efficacy of Esperoct in the general population of PUPs appears principally acceptable and principally comparable to results presented for PTPs of the same age cohort, as long dosing is adequately adjusted.

However, pharmacokinetic data indicate a large proportion of PUPs with low IR, with possible implications regarding efficacy and safety. A low IR is a clinical concern as it implies a reduced availability of the drug product in the blood. Concludingly, although efficacy results in the general trial population were principally not concerning, a large subset of PUPs who did not develop inhibitory antibodies responded to primary exposure of Esperoct with a period of low IR of varying length that was associated to potentially reduced efficacy (see section 3.3.4. for details). The warning in section 4.4. stresses the risk of low IR in PUPs including the risk of reduced efficacy as well as the need to monitor patients and implement necessary steps in case bleeding control is not warranted.

Trials NN7088-3859, NN7088-3860 and NN7088-4595

New data from studies 3859, 3860 and 4595 were also submitted. However, in these studies no paediatric patients were followed and are thus considered supportive studies for the current submission regarding the intended extension to treat paediatric patients. Of note, reported results of these studies do not indicate any relevant impact on the B/R balance of Esperoct.

Trial NN7088-3859

Study 3859 was a multi-national trial evaluating safety and efficacy, including pharmacokinetics, of Esperoct when administered for treatment and prophylaxis of bleeding in patients with severe haemophilia A aged 12-66 years at inclusion in the trial. Study 3859 was ongoing during the assessment of the initial licensure of Esperoct and was considered the main study. For a detailed depiction and assessment of the study design please refer to the EPAR of the initial submission. In short, the trial comprised a main phase and two extension phases that followed on-demand treatment of 20-75 IU/kg as well as prophylactic doses of 50 IU/kg in a Q4D regimen or 75 IU/kg in a Q7D regimen. Co-primary objectives were the evaluation of the immunogenicity of N8-GP in previously treated patients with haemophilia A and the evaluation of the clinical efficacy of N8-GP in bleeding prophylaxis (number of bleeds during prophylaxis). Secondary objectives were the evaluation of clinical efficacy of N8-GP when treating bleeds in patients with haemophilia A and the evaluation of the safety of N8-GP when used for prevention of bleeds and treatment of bleeds in patients with haemophilia A.

The individual mean ABR (2.74 and 4.41 for Q4D and Q7D) as well as the poisson estimated ABR (2.35 and 4.39 for Q4D and Q7D) reported from the final study data are in line with data reported previously

for extension 2 (individual mean ABR: 2.88 and 4.45; poisson estimated ABR 2.6 and 4.43, for Q4D and Q7D, respectively). The rate of bleeds that resolved with ≤ 2injections remains comparable (93.9% and 91.7% in the previously reported extension 2 compared to 94.1% and 9.5% reported now for Q4D and Q7D, respectively). The same applies to the reported haemeostatic response with a success rate of 85.6% and 84% in the previously reported extension 2 compared to 85.4% and 82.7% reported now for Q4D and Q7D, respectively. Thus, the prophylactic effect following the Q7D schedule appears slightly worse regarding breakthrough bleeding events, but bleeds were treated mostly successfully irrespective of the prophylactic dosing schedule.

In summary, data of the completed study appear to confirm conclusions on efficacy as derived during initial licensure.

Trial NN7088-3860

Study 3860 was an efficacy and safety study during surgical procedures in patients with haemophilia A. Conclusions of the prior assessment as depicted in the available EPAR for the initial MAA are principally confirmed with the current submission, but it is reiterated that the four-point-scale for clinical evaluation of haemostatic response during surgery (primary endpoint) is considered rather vague and is highly dependent on the investigators´/surgeons´ individual experience. Results were therefore interpreted cautiously and assessed together with the results derived from more objective secondary endpoints.

Trial NN7088-4595

The mean ABR in adolescent and adult Chinese patients (2.55) appears comparable to the mean ABR concluded during the main (3.73) and extension phase (2.74) of study 3859. Similarly, a high treatment success rate for breakthrough bleeds (94.8%) that were mostly treated with ≤2 injections (94.2%) also indicates favourable efficacy in the investigated Chinese population. No impact on the existing licensure of Esperoct is concluded from reported results on efficacy.

2.4.3. Conclusions on the clinical efficacy

Trials 3885, 4410 and 3908

Presented data for studies 3885, 4410 and 3908 principally confirm that the long-term prophylactic treatment with N8-GP provides sufficient bleeding control in paediatric haemophilia A patients. The same applies regarding the control of breakthrough bleeds. Dosing recommendations were adjusted based on actual consumption data during the studies and efficacy data are not concerning. However, a mildly worse bleeding control is reported in older paediatric PTPs (21.3% of treatment failure) compared to the younger age group (10.4% of treatment failures).

Thus, efficacy data generally support the treatment of paediatric patients with N8-GP. The large proportion of PUPs with low IR values is to be noted, as these were also associated with reduced efficacy (see PK discussion). The risk of low IR in PUPs, including the risk of reduced efficacy as well as the need to monitor patients and implement necessary steps in case bleeding control is not warranted, is stressed in section 4.4. of the SmPC.

Trials 3859, 3860 and 4595

Presented data for adolescent and adult subjects in studies 3859 and 3860 confirm conclusion from the initial licensure regarding dosing results from different dosing schedules (Q4D with 50IU/kg and Q7D with 75 IU/kg) as well as for bleeding control during surgical procedures in patients with haemophilia A. Efficacy data from Chinese patients in 4595 also confirm the prophylactic efficacy and the use as bleeding control for breakthrough bleeds. In summary, presented data appear to confirm conclusions on efficacy as derived during initial licensure and no impact on the B/R balance of Esperoct is concluded.

2.5. Clinical safety

Introduction

In the European Union (EU), Esperoct (turoctocog alfa pegol) received a marketing authorisation on 20 June 2019 for the treatment and prophylaxis of bleeding in patients aged 12 years and above with haemophilia A (congenital factor VII deficiency). The safety profile during the initial evaluation of the product revealed the following:

- The most common side effects observed in clinical trials were injection site reactions, rash, erythema and pruritus. Hypersensitivity (allergic) reactions occurred with Esperoct at an uncommon frequency (affecting up to 1 in 100 subjects). These include swelling, burning and stinging at the injection site, chills, flushing, itchy rash, headache, hives, low blood pressure, lethargy, nausea and vomiting, restlessness, a rapid heartbeat, tightness of the chest, tingling and wheezing. In some cases these reactions were severe. Very rarely, patients may develop antibodies against hamster protein in the medicine and have allergic reactions.
- At the time of the marketing authorisation there was a major uncertainty regarding long-term exposure to PEG. It was unknown if potential accumulation in various organs and tissues could have relevant clinical consequences. The potential clinical impact on brain development in children e.g. on cognitive, functional or metabolic properties was considered to be of particular concern.
- Available safety data derived in clinical trials with turoctocog alfa pegol, although limited with regards to the number of patients, treatment duration and absence of specific monitoring for PEG-associated adverse events, did not reveal any signals hinting to negative effects of PEG accumulation.
- Published data from long-term nonclinical studies with other PEGylated proteins have shown vacuolation in macrophages and in cells of excretory organs like the kidney, liver and choroid plexus.

Based on evidence presented in the initial dossier, a possible impact of accumulation of PEG on function of affected tissues/organs after long-term treatment could not be excluded with reasonable certainty. In consequence, the label was granted for adults and children ≥12 years of age, in whom most neurodevelopmental milestones are already reached.

The MAH has gathered additional data to support the extension of the indication to children below 12 years of age. The following data are updated or new in the current submission:

- Trial 3885 – a phase 3 trial in previously treated children <12 years of age (main + extension phase). During the initial submission data from the main phase was submitted and in the current application results of final analysed data from main + extension phase are included.
- Trial 3908 – a phase 3a trial in previously untreated children <6 years of age. An interim report was submitted during the initial submission, while the current application includes the final analysed data from the complete trial.
- Trial 3859 – a phase 3 trial in adolescent and adult PTPs ≥12 years of age (main + two extension phases). An interim report was submitted during the initial submission, while the current application includes the final analysed data from the complete trial.
- Trial 3860 – a phase 3 surgery trial in PTPs ≥12 years of age. During the initial submission an interim report was submitted and in the current application results of final analysed data are included.

As compared to the initial MAA submission in 2018, data from the following trials are also included in this application:

- Trial 4410 – a phase 3b long-term efficacy and safety trial in previously treated patients (PTPs) of all age groups. This trial was initiated after submission of the initial MAA application and completed post approval in the EU. Additional data on long-term safety and efficacy of N8-GP was obtained by recruiting patients from previous trials 3859 and 3885.
- Trial 4595 – phase 3b trial in adolescent and adult Chinese PTPs (≥12 years). Data from this trial is not pooled with the other ≥12 years PTPs since the trial was conducted in a cohort of Chinese adolescent and adult patients post initial MAA approval in the EU. Data from this trial is included only in PK and safety sections to support relevant results.

Overall safety summary strategy

Definitions

- An exposure day (ED) is defined as a day where at least one N8-GP dose was administered. This includes administration for treatment of bleeds, prophylaxis, surgery or for PK evaluations.
- Treatment-emergent adverse events are defined as any adverse events which occurred after N8-GP administration. Only treatment-emergent adverse events are included in this summary of clinical safety. Treatment-emergent adverse events are hereinafter referred to as adverse events.
- The presentation of safety data in this summary is based on the safety analysis set, which includes all patients who received at least one dose of N8-GP.

The following events were considered to be medical events of special interest in the N8-GP clinical trials:

- Medication errors
- Inhibitor formation against FVIII
- Allergic reaction including anaphylactic reactions
- Thromboembolic events

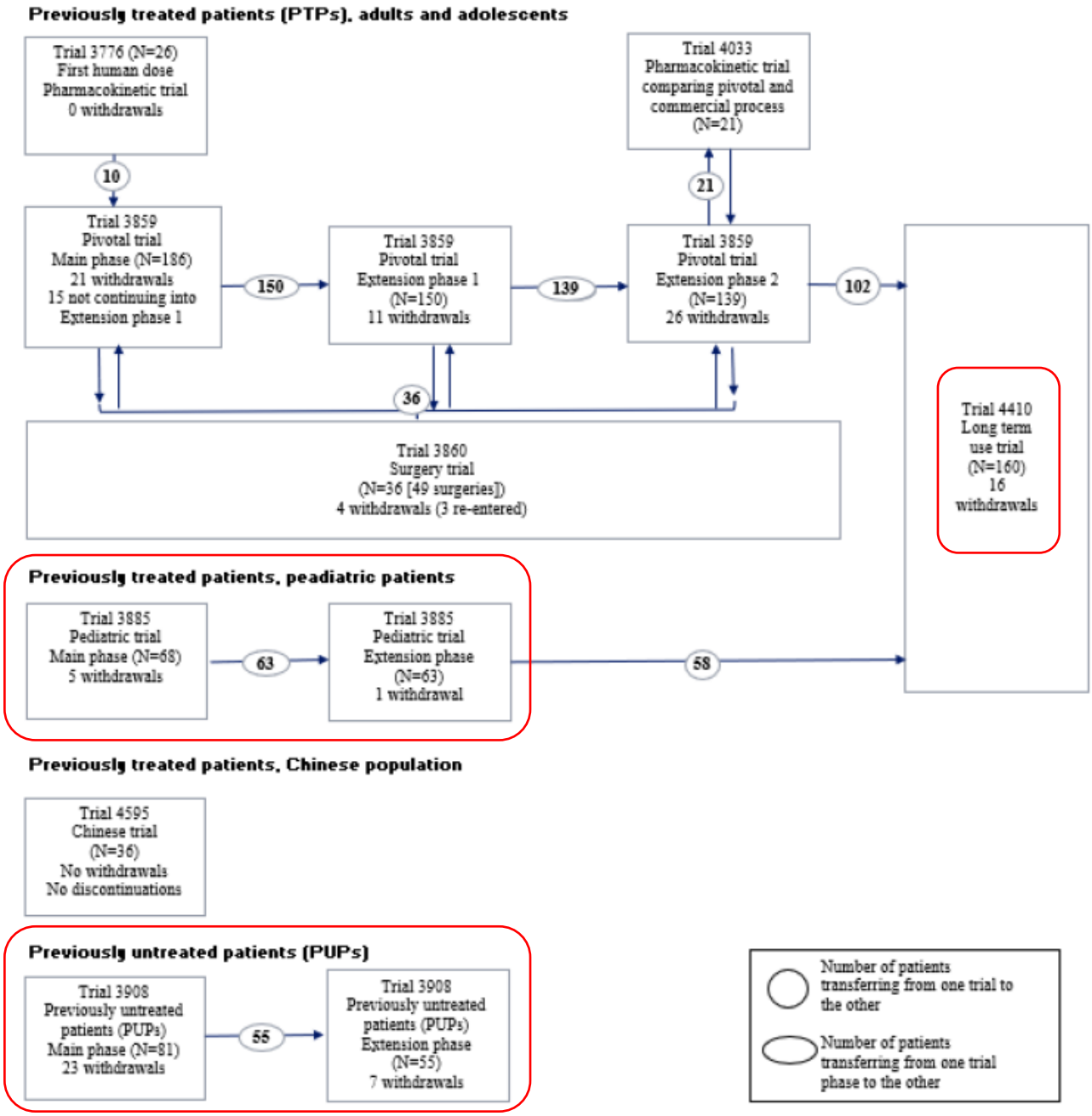
Grouping and pooling of data

- Safety data have been pooled from all completed trials in PTPs (trials 3776, 3859, 4033, 3885 and 4410) and presented for children (0-5 years and 6-11 years of age), adolescents (12-17 years of age) and adults (≥18 years of age). Safety results from the surgery trial (trial 3860), safety in PUPs (trial 3908) and in Chinese PTPs (trial 4595) was not pooled and is presented separately.
- Safety in PUPs is described separately and not pooled with PTPs due to different population characteristics. Safety information from Chinese patients is presented separately and has not been pooled with the global trial data for reasons outlined in Section 1.2.1. Patients undergoing major surgery will be in a different medical condition compared to patients on prophylaxis and on-demand treatment, and as expected, a different adverse event pattern is seen during surgery (trial 3860 and 4410). Therefore, safety during surgery is presented separately and not included in the pooled analysis, except for calculation of inhibitor rate.
- Clinical laboratory evaluations, vital signs and physical examinations are described on a trial-by-trial basis.
- For exposure, baseline demographics and adverse events (overall, SAEs, by relation to trial product and by severity), results in the pool of PTPs are presented by age at trial entry (younger children 0-5 years, older children 6-11 years, adolescents 12-17 years and adults ≥18 years). For the most commonly reported adverse events, results are presented by baseline and actual age of the patient at the onset of the AE.
- Safety results from trial 3908 in PUPs aged less than 6 years are presented separately for all applicable assessments throughout this safety summary.

- A total of 6 previously treated children were below 2 years of age at the time of inclusion in the clinical programme. Safety in these patients is described separately.

Patient exposure

Figure 14: Flow of patients in the N8-GP clinical development programme



The figure shows the flow of patients through the trials. Prior to entering the extension phase(s) of the trials, patients had to re-consent to continue. Those who did not re-consent are denoted as 'not continuing' in the figure.
All the patients enrolled in trials 3860 and 4033 were recruited from trial 3859 and re-entered trial 3859 upon completion of trial 3860 or trial 4033. Four (4) patients withdrew from trial 3860 as they had their surgery postponed/cancelled of whom 3 (3) patients re-entered trial 3860 to have surgery done at a later stage. Eleven (11) patients entered trial 3860 more than once from different phases of trial 3859.
Abbreviation: N: Number of exposed patients.
Red Frame: Trials of special relevance for this submission.

In the clinical development programme of N8-GP, overall 68 unique previously treated children have been exposed to N8-GP in the clinical trials 3885 and 4410 for a total of 43,698 EDs, corresponding to a total of 414.9 PYE; younger children (0-5 years) had a total of 19,759 EDs, corresponding to a total of 188.6 PYE and older children (6-11 years) had a total of 23,939 EDs, corresponding to a total of 226.3 PYE across trials (Summary 2.7.4, Table 1-2).

When exposure is calculated for prophylaxis treatment in previously treated children (trials 3885 and 4410), younger children (0-5 years) had a total of 19,759 EDs and older children (6-11 years) had a total of 23,936 EDs across trials, which corresponds to a total of 188.3 and 226.1 PYE, respectively.

Across all the pooled **trials in PTP children** (3885 and 4410), the mean (SD) dose of N8-GP used for the treatment of all bleeds from start to stop was 94.9 (73.1) IU/kg and 87.1 (56.1) IU/kg in younger (0-5 years) and older (6-11 years) children, respectively. The mean amount of N8-GP used to treat bleeds was higher for patients <18 years of age than patients ≥18 years of age. The mean amount of N8-GP used by children was higher than the per-protocol specified dose range (20−75 IU/kg) as some patients had bleeds requiring more than one injection to be controlled.

In trial **3908 (PUPs),** a total of 81 patients (including main phase + extension phase + ITI treatment) were exposed for 18,184 EDs corresponding to a total of 233.8 PYE. Excluding the ITI treatment, the 81 patients were exposed to 16,670 EDs corresponding to a total of 224.3 PYE. A mean and median of 207.0 and 154.0 doses were recorded per patient, respectively, ranging from 1 to 792.0 doses per patient. The vast majority of treatment with N8-GP was provided while patients were on prophylaxis where the mean number of EDs per patient was 235.4 EDs, while patients on pre-prophylaxis had a mean of 7.8 EDs

Through the N8-GP clinical development programme, 201 patients have been exposed for more than 2 years, 192 patients have been exposed for more than 3 years, 178 patients have been exposed for more than 5 years, 109 patients have been exposed for more than 7 years, and 27 patients (no children) have been exposed for more than 8 years. Of the total 68 unique previously treated children, 59 were exposed for more than 5 years, 55 were exposed for more than 6 years and 21 children for more than 7 years.

Figure 15: Duration of exposure to N8-GP by age group – trials in PTPs – safety analysis set

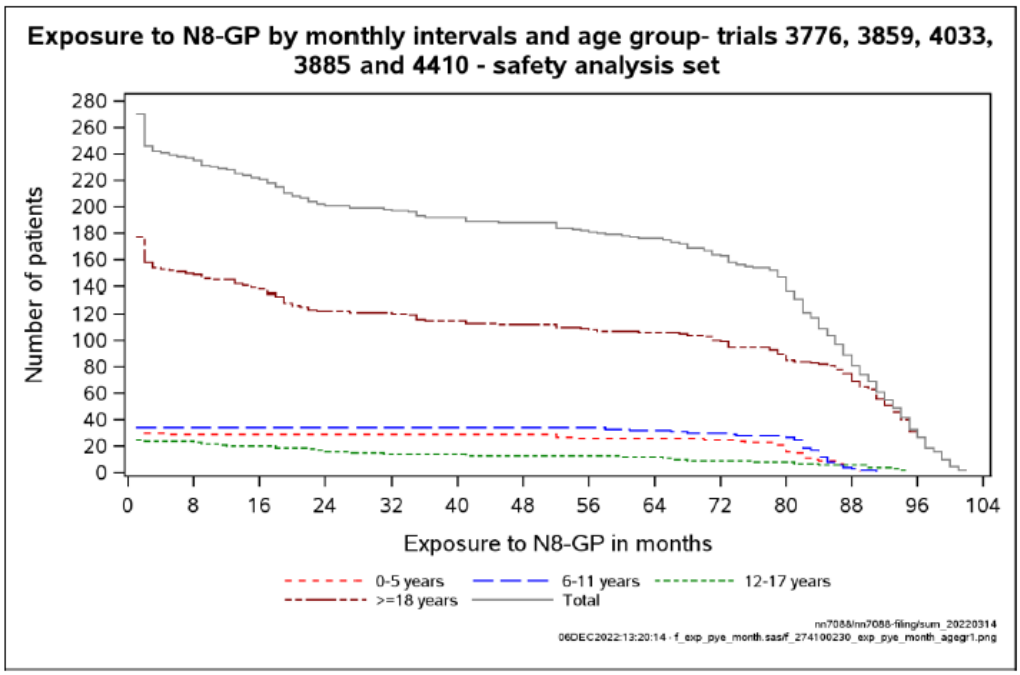


Figure 16: Cumulative exposure to N8-GP by trial and age group – trials in PTPs – safety analysis set

Trial Age group	Number of patients	Patient years of exposure	Exposure days
Trial 3776			
>=18 years	26	1.77	26
Total	26	1.77	26
Trial 3859			
12-17 years	25	89.69	7654
>=18 years	161	695.72	58923
Total	186	785.41	66577
Trial 4033			
>=18 years	21	1.93	127
Total	21	1.93	127
Trial 3885			
0-5 years	34	138.98	14596
6-11 years	34	166.73	17542
Total	68	305.72	32138
Trial 4410			
0-5 years	26	49.63	5163
6-11 years	32	59.57	6397
12-17 years	8	14.55	1131
>=18 years	94	174.46	16007
Total	160	298.22	28698
All Trials			
0-5 years	34	188.61	19759
6-11 years	34	226.3	23939
12-17 years	25	104.24	8785
>=18 years	177	873.89	75083
Total	270	1393.0	127566

An exposure day (ED) 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.

Adverse events

Commen Adverse Events -PTPs

Of the total 3197 reported adverse events in all age groups, 1098 adverse events were reported in 67 children. The majority (n=1075) of the adverse events reported in children were assessed as non-serious and 23 adverse events in 19 children were assessed as serious (see below for details on serious adverse events). Of the total 1098 adverse events reported in children 932 adverse events were mild, 150 were moderate and 16 were severe.

In the adolescent patients (12–17 years), the rate of adverse events per PYE was slightly higher than in children (0-5 years and 6-11 years) and adults (>18 years): 3.07 versus 2.96 (0–5 years), 2.38 (6-11 years) and 2.04 (≥18 years). However, the overall adverse event pattern in adolescents did not raise any safety concern; this age group did not have higher rates of serious adverse events, severe adverse events or events judged as possibly or probably related to N8-GP administration compared to the other age groups. The rate of adverse events was higher in younger children (0–5 years) than in older children (6–11 years). As expected, this difference was mainly driven by frequent adverse events concerning common diseases in small children (e.g., nasopharyngitis and cough) and did not raise any safety concern.

In previously treated children, the most commonly reported adverse events by PTs (reported in >5% of patients) in patients aged 0-5 years were 'epistaxis' (57 events in 4 [11.8%] patients), 'cough' (30 events in 15 [44.1%] patients), 'nasopharyngitis' (23 events in 12 [35.3%] patients), 'upper respiratory tract infection' (21 events in 10 [29.4%] patients), 'pyrexia' (19 events in 9 [26.5%] patients) and in patients aged 6-11 years were 'upper respiratory tract infection' (39 events in 13 [38.2%] patients), 'nasopharyngitis' (24 events in 13 [38.2%] patients), 'headache' (18 events in 9 [26.5%] patients), 'gastroenteritis' (15 events in 10 [29.4%] patients), 'pain in extremity' (13 events in 7 [20.6%] patients) and 'limb injury' (13 events in 5 [14.7%] patients). When analysed across all age groups, the most commonly reported adverse events were 'nasopharyngitis', 'upper respiratory tract infection', 'headache', 'arthralgia', 'cough', 'influenza', 'diarrhoea', and 'pyrexia'.

A total of 102 adverse events in 47 (17.4%) patients were evaluated by the investigator as possibly or probably related to N8-GP corresponding to a rate of 0.07 events per PYE. The majority of the events judged as possibly or probably related to N8-GP across all age groups were non-serious, of mild or moderate severity and the majority of the patients recovered from their events.

A total of 21 adverse events in 14 children were evaluated by the investigator as possibly or probably related to N8-GP, corresponding to a rate of 0.07 and 0.04 events per PYE in younger children (0-5 years) and older children (6-11 years) respectively. All the adverse events (by PT) evaluated as possibly or probably related to N8-GP by the investigator in children were reported in single patients (2.9%); except for one related event of seizure which was reported in 2 (5.9%) patients. In comparison, none of the adverse events possibly or probably related to N8-GP were reported in more than 1 (4%) adolescents (12-17 years) and in more than 6 (3.6%) adults (>18 years). Across the age-groups, the most frequently reported related events were by symptoms were 'headache' (4 events in 4 patients), 'rash' (6 events in 3 patients), 'arthralgia' (3 events in 3 patients), 'dizziness' (2 events in 2 patients), and 'seizure' (2 events in 2 patients). The events related to laboratory investigations were 'aspartate aminotransferase increased' (9 events in 7 patients), 'alanine aminotransferase increased' (9 events in 7 patients) and 'gamma-glutamyl transferase increased' (2 events in 2 patients). Other events judged as possibly or probably related to N8-GP by the investigator were reported as single events across different SOCs or as few events of the same PT in 1 patient.

Table 56: Overview of adverse events by age group – trials in PTPs – safety analysis set

	0-5 years		6-11 years		12-17 years		>=18 years		Total	
	N(%)	E[R]	N(%)	E[R]	N(%)	E[R]	N(%)	E[R]	N(%)	E[R]
Number of patients	34		34		25		177		270	
Patient years of exposure	188.62		226.31		104.24		873.88		1393.1	
Exposure days	19759		23939		8785		75083		127566	
All adverse events	33(97.1)	559[2.96]	34(100)	539[2.38]	25(100)	320[3.07]	151(85.3)	1779[2.04]	243(90.0)	3197[2.29]
Serious adverse events	12(35.3)	15[0.08]	7(20.6)	8[0.04]	5(20.0)	6[0.06]	40(22.6)	75[0.09]	64(23.7)	104[0.07]
Non serious adverse events	33(97.1)	544[2.88]	34(100)	531[2.35]	24(96.0)	314[3.01]	151(85.3)	1704[1.95]	242(89.6)	3093[2.22]
Severity										
Mild	29(85.3)	453[2.40]	33(97.1)	479[2.12]	22(88.0)	276[2.65]	144(81.4)	1298[1.49]	228(84.4)	2506[1.80]
Moderate	27(79.4)	94[0.50]	21(61.8)	56[0.25]	15(60.0)	40[0.38]	111(62.7)	406[0.46]	174(64.4)	596[0.43]
Severe	9(26.5)	12[0.06]	4(11.8)	4[0.02]	4(16.0)	4[0.04]	37(20.9)	74[0.08]	54(20.0)	94[0.07]
Missing		-		-		-	1(0.6)	1[0.00]	1(0.4)	1[0.00]
Relationship										
Probably or possibly	8(23.5)	13[0.07]	6(17.6)	8[0.04]	4(16.0)	8[0.08]	29(16.4)	73[0.08]	47(17.4)	102[0.07]
Unlikely	31(91.2)	541[2.87]	34(100)	531[2.35]	25(100)	311[2.98]	151(85.3)	1705[1.95]	241(89.3)	3088[2.22]
Missing	1(2.9)	5[0.03]		-	1(4.0)	1[0.01]	1(0.6)	1[0.00]	3(1.1)	7[0.01]
Adverse events										
Leading to withdrawal	2(5.9)	2[0.01]		-	1(4.0)	1[0.01]	4(2.3)	4[0.00]	7(2.6)	7[0.01]

N: Number of patients with adverse event. %: Percentage of patients with adverse event. E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/patient years of exposure)
An exposure day (ED) 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.

Common adverse events – PUP trial 3908

Of total 81 patients, 78 (96.3%) patients experienced 760 adverse events, corresponding to an adverse event rate of 3.39 events per PYE during the trial.

The majority of adverse events (631 events) were evaluated as mild, while 98 events were moderate, and 31 events were severe. Most events (726 events) were recovered/resolved while 23 events were not recovered/resolved. There were no adverse events with fatal outcome. There were 7 adverse events leading to withdrawal of 6 patients during the trial.

Of the total 760 adverse events, 80 events in 48 (59.3%) patients were reported as serious adverse events. Twenty-seven (27) serious events were reported as severe, 25 events as moderate and 28 events as mild in intensity. Majority of the events were reported as unlikely related (53 events) and 27 events in 26 patients were judged as probably or possibly related to N8-GP by the investigator. Five (5) serious events in 5 patients led to withdrawal of trial product ('factor VIII inhibition', 'vaccination site haemorrhage', 'anti factor VIII antibody positive', 'heart rate increased' and 'factor VIII inhibition').

The 5 most commonly reported adverse events were:

- 'Nasopharyngitis' (87 events in 27 patients; 0.39 adverse events per patient year in trial)
- 'Pyrexia' (83 events in 32 patients; 0.37 adverse events per patient year in trial)
- 'Contusion' (78 events in 6 patients; 0.35 adverse events per patient year in trial)
- 'Upper respiratory tract infection' (43 events in 20 patients; 0.19 adverse events per patient year in trial)

Serious adverse event/deaths/other significant events

Trials in PTPs

A total of 104 serious adverse events were reported in 64 (23.7%) patients, corresponding to a rate of 0.07 serious adverse events per PYE.

Of the 104 events, 23 events were reported in 19 (27.9%) children and were all reported as recovered/ resolved. Of these 23 events, 15 events were reported in 12 (35.3%) patients aged 0-5 years, corresponding to a rate of 0.08 events per PYE and 8 events were reported in 7 (20.6%) patients aged 6-11 years, corresponding to a rate of 0.04 events per PYE. Fifteen (15) serious events were severe, 6 were moderate and 2 were mild in severity. Majority of the serious events (19 events) All the patients continued with N8-GP treatment, except for 1 patient with 'haemorrhage' (described below). were unlikely related to N8-GP and 4 were possibly or probably related to N8-GP by the investigator.

Across age groups, the serious adverse events were mostly recorded as single events and across different SOCs. The serious adverse events occurred after 2–473 EDs of N8-GP, and no association between frequency of the events and exposure time was observed. Majority of the patients recovered from their serious adverse events, while 2 events in 2 adult PTPs had a fatal outcome and 11 events had an outcome stated as 'not recovered' (e.g. Aortic valve stenosis, cerebral infarction, FVIII inhibition, all in adult or adolescent patients).

Of the 104 serious adverse events, 6 events including 4 events in children, were judged as possibly or probably related to N8-GP by the investigator ('intervertebral discitis', 'factor VIII inhibition', 'hypersensitivity', 'haemorrhage', and 'seizure' [2 events]). The remaining serious adverse events were judged as unlikely related to N8-GP by the investigator.

The event 'haemorrhage' is described below:

- A -year-old male patient (trial 3885) had an event of 'haemorrhage' reported as a serious adverse event. On , the patient developed a large, traumatic haematoma over the (superficial) one week after commencing treatment with N8-GP. On further treatment with N8-GP for 2 consecutive days, the event began to resolve. The patient also developed increasing bruising around his port-a-cath and torso over the following few days. On , the patient was found to have a soft tissue/muscle bleed affecting the arm, which appeared to be spontaneous. The patient was treated with N8-GP and local blood tests were sent. During this time there were no concomitant medications, and patient was in good condition. Blood tests revealed a normal platelet and eosinophil count, and local inhibitor screen was negative. N8-GP levels at 24 hours post 1000 units were <1. Inhibitor test was <0.6 BU/ml. The patient was withdrawn from the trial and treatment. On , the patient was treated with Kogenate 500 units daily; his symptoms settled, and he remained well and symptom free since then. Laboratory studies showed a 48-hour trough FVIII of 2% (post 500 units Kogenate).

Table 57: Serious adverse events possibly or probably related to N8-GP as judged by the investigator – trials 3776, 3859, 4033, and 4410

Patient ID/ Trial	Age	Preferred term	ED	Relationship	Severity	Outcome
[redacted] / 3859	[redacted]	Intervertebral discitis	60	Possible	Severe	Recovered
[redacted] / 3859	[redacted]	Factor VIII inhibition	97	Probable	Moderate	Not recovered
[redacted] / 3885	[redacted]	Haemorrhage	4	Probable	Moderate	Recovered
[redacted] / 3885	[redacted]	Hypersensitivity	4	Probable	Severe	Recovered
[redacted] / 4410	[redacted]	Seizure	159	Possible	Severe	Recovered
[redacted] / 4410	[redacted]	Seizure	10	Possible	Severe	Recovered

Note: Relationship is based on Investigator's causality

Abbreviation: ED = exposure day

PUP trial 3908

A total of 80 serious adverse events were recorded in 48 (59.3%) patients corresponding to an overall rate of 0.36 serious adverse events PYE. Twenty-seven of the serious adverse events were judged as probably or possibly related to N8-GP by the investigator of which 22 serious adverse events alone were reported with PT 'factor VIII inhibition'. Seventeen (17) of these 27 events were recovered/resolved, and 1 event was recovered/resolved with sequelae. Out of remaining 9 events, outcome was unknown for 2 events and not recovered/not resolved for remaining 7 events. A total of 5 serious adverse events were reported as life-threatening ('intracerebral haemorrhage' [2 events], 'spinal epidural haematoma', 'wound haemorrhage', and 'FVIII inhibition'). All these events were considered as unlikely related to N8-GP except for 'FVIII inhibition' that was considered as possibly related to N8-GP.

Deaths

No fatal events were reported in children (both PTPs and PUPs) in the N8-GP development program.

Two (2) deaths were reported in adult patients (PTPs) in the N8-GP clinical trials:

- A fatal event of 'pancreatic carcinoma metastatic' was reported in one patient (trial 3859). The event was reported after 88 days of exposure to N8-GP. The patient complained of unexplained weight loss of 10 kg during the past few months and abdominal pain leading to hospitalisation due to suspicion of malignant tumour. Findings were compatible with a liver metastasis of a pancreatic cancer or with a cholangiocellular carcinoma. The patient started treatment with chemotherapy (gemcitabine).

Approximately 6 months later, the patient came to the emergency room due to haematemesis. The patient was treated with omeprazole magnesium and unspecified crystalloid fluids. He became unconscious, saturation decreased, and massive hematemesis occurred. Due to the underlying disease no resuscitation was performed, and the patient died. The event was considered unlikely to be related to N8-GP by the investigator and Novo Nordisk.

- A fatal event of 'malignant melanoma' was reported in one patient (trial 4410). The event was reported after 118 days of exposure to N8-GP. The patient had a history of hepatitis C and concurrent conditions included haemophilia arthropathy, hypertension and mild fibrosis of liver. The patient was diagnosed with malignant melanoma during the trial. The patient was hospitalised with elevated liver enzymes, loss of appetite and fatigue. A CT scan showed hepatomegaly, enlarged lymph nodes, pulmonary infiltration in both lungs and severe arthrosis in both hips. The patient was treated with NovoEight during hospitalisation which resulted in withdrawal from the study. Two (2) days later patient died due to malignant melanoma. Post-mortem liver biopsy showed metastasis from melanoma. The event was considered unlikely to be related to N8-GP by the investigator and Novo Nordisk.

AESIs

Medication errors - trials in PTPs

In order to ensure that all potential medication errors were captured, an SMQ search was performed. A total of 9 medication errors were identified in 9 patients and comprised 'product preparation error', 'overdose' and 'accidental overdose' reported in trial 3859; 'accidental overdose', 'device malfunction', 'drug administration error' and 'medication error' reported in trial 3885; and 'device malfunction' and 'medication error' in trial 4410. Of the 9 medication errors reported, 6 events were reported in children and the rate of events per PYE were comparable between children and adults. All events of medication errors were non-serious, mild and the outcome was stated as recovered. No associated adverse events were reported with any of the medication errors.

The highest dose that was administered in error was administered to a child:

A child was prescribed 4 mL of 2000 IU vial N8-GP. The patient was dosed in error with 8 mL of 2000 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. The FVIII activity level post overdose was shown to be 285% (Trial 3885). The patient recovered the same day. Thus, no symptoms associated with the overdose of N8-GP were reported.

Medication errors – PUP trial 3908

There were no medication errors reported in PUP trial 3908.

Allergic reactions - trials in PTPs

In order to ensure that all events were captured, searches were made in the dataset using both a narrow and a broad scope NNMQ search 'allergic-type hypersensitivity reactions'.

A total of 105 adverse events in 66 (24.4%) patients were identified in the narrow search for allergic reactions. The most frequently reported events by PT were 'rash' (32 events in 21 [7.8%] patients), 'eczema' (20 events in 15 [5.6%] patients), 'urticaria' (12 events in 11 [4.1%] patients), and 'rhinitis allergic' (6 events in 6 [2.2%] patients). Fifty-six (56) out of 105 adverse events of allergic reactions

were reported in 29 (42.6%) children. The most commonly reported events in children were similar to the events reported in adolescent and adult patients.

The majority of the adverse events related to allergic reactions identified in the search were non-serious, of mild or moderate severity and judged as unlikely related to N8-GP by the investigator. Two adverse events of 'circulatory collapse' and 'hypersensitivity' were judged to be severe, and these events were reported as serious adverse events.

One (1) serious adverse event of 'hypersensitivity' in a child was judged as probably related to N8-GP was reported:

- A very yound child had an event of 'hypersensitivity' reported as a serious adverse event. The patient was withdrawn from the trial as he met the withdrawal criterion 'allergy/anaphylaxis related to trial product'. The patient developed a mild type 1 allergic reaction after the first N8-GP dose and later a severe allergic reaction after the fourth N8-GP dose. Neither the mild, nor the severe allergic reaction required any treatment or systemic intervention and the clinical symptoms resolved after 2 hours. The patient had received N8-GP for a total of 4 EDs at the time of withdrawal. Other than low titre pre-existing antibodies to PEG, which decreased in titre over time, no antibodies of IgM, IgG or IgE isotypes directed against N8-GP or CHO HCP were detected. IgE antibodies to PEG were not detected. Subsequently the patient showed a similar reaction pattern after switching treatment to a non-PEGylated rFVIII product indicating that PEG was not the inducing factor. The second injection with the FVIII product was accompanied with vomiting similar to what led to the patient's withdrawal from N8-GP. The investigator could not exclude gastrointestinal disorder. At the last follow-up, the patient was still on the same FVIII product with 1–3 times weekly home injections and has had multiple injections after the withdrawal from the trial.

A total of 9 adverse events related to allergic reactions reported in 5 patients, of which, 6 adverse events reported in 3 children, were judged as possibly or probably related to N8-GP by the investigator; all non-serious and of mild or moderate severity, except 1 serious adverse event of 'severe hypersensitivity' (described above) (Table 58).

Table 58: Allergic reactions possibly related to N8-GP as judged by the investigator – identified in narrow NNMQ search

I	Age	Preferred term	ED	Relationship	Severity	Serious	Outcome
	[redacted]	Rash	1	Probable	Moderate	No	Recovered
		Rash	123	Probable	Mild	No	Recovered
	[redacted]	Rash	22	Possible	Mild	No	Recovered
	[redacted]	Dermatitis	490	Possible	Mild	No	Recovered
	[redacted]	Hypersensitivity	1	Probable	Mild	No	Recovered
		Hypersensitivity	4	Probable	Severe	Yes	Recovered
	[redacted]	Rash	68	Possible	Mild	No	Recovered
		Rash	72	Possible	Mild	No	Recovered
		Rash	79	Probable	Mild	No	Recovered

Abbreviation: ED = exposure day

Allergic reactions – PUP trial 3908

A total of 24 events (2.24 adverse events per PYE) in 17 (21.0%) patients were identified in the narrow search for allergic reactions:

- 14 events in 11 patients were within SOC 'skin and subcutaneous tissue disorders' distributed as 8 different PTs ('eczema', 'urticaria', 'dermatitis atopic', 'dermatitis contact', 'angioedema', 'rash', 'rash erythematous', and 'rash maculo-papular').
- 10 events were distributed on 5 SOCs and 6 PTs ('blepharitis allergic', 'conjunctivitis allergic', 'lip swelling', 'catheter site rash', 'drug hypersensitivity', and 'rhinitis allergic').
- Of the total 24 adverse events, majority were mild (21 events) and assessed as unlikely (21 events) related to N8-GP by the investigator. The outcome for 19 adverse events was reported as recovered. Two (2) serious adverse events of 'rash erythematous' and 'angioedema' were reported in 1 patient, both events were of moderate intensity and considered as unlikely related to N8-GP.

One inhibitor patient (22 EDs) experienced severe drug hypersensitivity (allergy to FVIII) which was assessed as possibly related to N8-GP. The patient had an allergy test with several FVIII concentrates including N8-GP and it showed that patient had allergy to all FVIII. The patient was withdrawn from the trial due to the event as the patient was not able to be treated with N8-GP.

The MAH assessed the majority of the events identified in the narrow NNMQ search as explained by alternative aetiologies and/or without establishment of a timely causal association. A minority of the events were assessed to be possibly or probably related to N8-GP. Based on the MAH assessment, rash, erythema, pruritus and hypersensitivity are considered adverse drug reactions.

Injection site reactions - trials in PTPs

Injection site reactions are known to occur with injection of FVIII products. Potential injection site reactions were identified through an NNMQ.

A total of 8 adverse events concerning injection site reactions were identified in 8 patients. Of the 8 events, 1 event of injection site reaction (PT: 'injection site swelling') was reported in a child. The events were reported as 'infusion site reaction', 'injection site reaction', 'injection site erythema', 'injection site rash', 'vessel puncture site haematoma' and 'vessel puncture site pain' (trial 3859) and 'injection site swelling' (trial 3885). All the events were non-serious, of mild or moderate severity and all patients recovered from the events.

Injection-site reactions are an inherent potential risk when administering a drug intravenously and are commonly related to the injection technique. 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. Three (3) of the events ('injection site reaction' and 'injection site thrombosis' in trial 3859 and 'injection site swelling' in trial 3885) were judged by the investigator as possibly or probably related to N8-GP.

Injection site reactions – PUP trial 3908

A total of 2 adverse events concerning injection site reactions were identified in 2 patients. The events were reported as 'injection site swelling' and 'vessel puncture site haematoma'. Both events were possibly or probably related to N8-GP, with mild or moderate in severity and the patients recovered from the events.

Thromboembolic events - trials in PTPs

In all clinical trials with N8-GP, thromboembolic events were to be reported as medical events of special interest. In order to ensure that all events were captured, an SMQ search of 'embolic and thrombotic events' was performed; the PTs in the search are presented in Appendix 7.1, Listing 88.

No thromboembolic events were reported in children in trials 3885 and 4410.

Two (2) thromboembolic events were reported in adult PTPs within SMQ category of 'embolic and thrombotic events':

- A patient (trial 3859) had a serious adverse event of 'suspicion of cranial micro infarction' following cranial magnetic resonance imaging (coded to PT 'cerebral infarction'). However, there was no definitive diagnosis and relationship to N8-GP was recorded as unlikely by the investigator and by the MAH. The event was recorded following 168 EDs with N8-GP. The patient continued treatment with N8-GP. The outcome of the adverse event was stated as 'not recovered'. Concurrently, a suspected cerebral microhaemorrhage was reported for the patient. The investigator reported the underlying disease (haemophilia), vasculitis, and post infection as alternative aetiologies for the 2 events cerebral microhaemorrhage and cerebral infarction.
- A patient (trial 3859) had a non-serious adverse event of 'injection site thrombosis'. The event was recorded following 619 EDs with N8-GP. The patient continued treatment with N8-GP. The outcome of the adverse event was stated as 'recovered'. The investigator considered the event as possibly related to N8-GP.

Thromboembolic events – PUP trial 3908

A total of 3 events (0.02 adverse events per PYE) in 2 (2.5%) patients were within SMQ category thromboembolic events: PTs 'shunt occlusion', 'device occlusion' and 'central venous catheterisation' and outcome for all 3 events was reported as recovered. All 3 thromboembolic adverse events reported were related to devices and procedures used in patients with haemophilia and were assessed as unlikely related to N8-GP by the investigator.

Based on the extensive data from nonclinical and clinical studies, the MAH contends that thromboembolic events do not constitute a safety concern for N8-GP. This is supported by the literature which documents that thrombotic complications in patients with haemophilia A are very rare, even in those at high risk of thrombosis[1]. Moreover, the risk of thrombotic complications with high purity FVIII products, such as N8-GP, is judged to be low[2].

1 Sousos N, Gavriilaki E, Vakalopoulou S, Garipidou V. Understanding cardiovascular risk in hemophilia: A step towards prevention and management. Thromb Res. 2016;140:14-21.

2 Coppola A, Franchini M, Makris M, Santagostino E, Di Minno G, Mannucci PM. Thrombotic adverse events to coagulation factor concentrates for treatment of patients with haemophilia and von Willebrand disease: a systematic review of prospective studies. Haemophilia. 2012;18(3):e173-87.

Adverse events related to the theoretical safety concern of PEG

The SMQ searches 'acute renal failure' and 'drug-related hepatic disorders' were chosen because the kidneys and the liver are known sites of PEG elimination. The NNMQ search 'CNS events' consisting of the SOCs Nervous system disorders and Psychiatric disorders was chosen based on nonclinical studies.

Drug-related hepatic disorders - trials in PTPs

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, a total of 120 (44.4%) patients were hepatitis C positive at baseline. Further, 6 (3.4%) patients were hepatitis B positive at baseline and half of them were also hepatitis C positive.

A total of 93 adverse events in 40 (14.8%) patients were identified in the SMQ search for 'drug related hepatic disorders'. The majority (24/40) of these patients were positive for hepatitis C and/or hepatitis B at baseline, which most likely explains the adverse events in these patients. Four (4) out of the 93 adverse events were reported in 4 children; these events ('hepatomegaly', 'hepatic steatosis', 'alanine aminotransferase increased', and 'blood alkaline phosphatase increased') were reported as mild in severity, unlikely related to N8-GP as judged by the investigator and resolved. The patients continued with N8-GP treatment and the events did not give rise to any new safety concern.

Overall, most events (67/93) were evaluated by the investigator as unlikely related to N8-GP (Appendix 7.1, Table 30). The remaining 26 events in 14 (5.2%) patients were judged as possibly or probably related to N8-GP by the investigator; all were non-serious and of mild (23 events) or moderate (3 events) severity, and the majority of the events had the outcome stated as recovered. Increased ALAT, ASAT and GGT were the most prevalent events.

Drug-related hepatic disorders – PUP trial 3908

One (1) non-serious adverse event of 'liver function test increased' was reported in the trial. The event was reported as moderate in severity, unlikely related to N8-GP by the investigator and recovered/ resolved. The patient continued with N8-GP treatment. No safety concerns were identified.

Overall, the adverse events concerning increased hepatic enzymes were transient and no apparent pattern in the distribution over time was identified. Thus, based on all available data there is no indication that long-term exposure may have a negative impact on liver function in haemophilia patients, and the overall risk for adverse events concerning hepatic disorders associated with N8-GP treatment is expected to be very low.

Renal disorders - trials in PTPs

A total of 8 adverse events concerning renal disorders were reported in 6 (2.2%) patients. Three (3) patients had 5 adverse events of 'blood creatinine increased'; 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. Two (2) out of 8 events were reported in 2 (5.9%) children; these were 'proteinuria' (non-serious, moderate in severity, possibly related to N8-GP by the investigator) and 'blood creatinine increased' (non-serious, mild in severity, unlikely related to N8-GP by the investigator). Both the events were reported as recovered and patients continued with N8-GP treatment.

Renal disorders – PUP trial 3908

No renal disorders as per SMQ search of 'acute renal failure' were reported in PUP trial 3908.

Central nervous system-related adverse events by baseline and actual age - PTPs

Central nervous system (CNS)-related adverse events constitute events under SOC 'nervous system disorders' and 'psychiatric disorders'.

A total of 43 CNS-related adverse events were reported in 22 (32.3%) children by age at trial entry. Of the total 43 CNS-related adverse events, 12 adverse events (0.06 events per PYE) were reported in 7 (20.6%) patients aged 0-5 years and 31 adverse events (0.14 events per PYE) were reported in 15 (44.1%) patients aged 6-11 years. Further, when summarised as per actual age group at the onset of event, a total of 23 CNS-related adverse events were reported in 16 (24.2%) patients. Of the total 23

CNS-related adverse events, 2 adverse events (0.03 events per PYE) were reported in 2 (5.9%) patients aged 0-5 years and 21 adverse events (0.11 events per PYE) were reported in 15 (25.4%) patients aged 6-11 years. The AE of 'headache' was reported in 2 patients in the younger age group (0-5 years).' In older children (6-11 years), the most common CNS-related AE was 'headache' (14 events in 10 patients) and 1 AE of 'post-traumatic headache' was reported.

Data showed that the proportion of patients who reported CNS-related adverse events was lower in younger children compared to older children, when analysed by baseline or by actual age groups.

A total of 9 serious adverse events were reported within the SOC 'nervous system disorders' in 8 patients, of which, 3 serious events were reported in 3 children ('seizure' [3 patients]):

- One event of seizure was reported in a patient. The patient had a medical history of cognitive disorder (not specified) which was treated with methylphenidate. Further, the patient experienced previous head bleed as a toddler which resulted in encephalomalacia, as reported by the investigator. There were no concurrent illness or trauma in relation to the event. Following this event, no reoccurrence or progression of seizures were reported. Patient continued to receive N8-GP. The event was assessed as possibly related to N8-GP by investigator. The MAH assessed this event as unlikely related to N8-GP based on the following: The medical history included a prior head bleed with resultant encephalomalacia comprising a possible seizure focus and increased risk of seizure. Further, the patient received methylphenidate which is known to cause convulsion (adverse reaction). The patient recovered and continued to receive N8-GP, and no reoccurrence of seizure was reported.
- A patient had generalised convulsion for approximately 2 minutes after collapsing from a chair after 159 EDs. The clinical evaluation, brain CT, electroencephalogram (EEG), magnetic resonance imaging (MRI) and cardiac exam were all normal with no abnormalities found. The repeat EEG performed 1 month after the event showed abnormal findings with showed sharp and slow like wave. The patient was treated with levetiracetam. There was no reoccurrence of the seizure, and he continued to receive N8-GP treatment. The event was assessed as possibly related to the N8-GP by the investigator.
- A patient experienced a seizure after an unwitnessed fall after 116 EDs. Patient had 2-3 min left gaze deviation and shaking of the left side of the body followed by 1-2 min of post-ictal confusion, without loss of bowel or bladder control. The head CT scan was normal, and the patient continued the trial drug without any changes. No antiepileptic medication was given, and there was no reoccurrence of seizures. The event was assessed as unlikely related to the N8-GP by the investigator.

Two (2) events within the SOC 'psychiatric disorders' were reported as a serious adverse events in 2 adult patients ('depression' and 'depression suicidal').

<u>Central nervous system-related adverse events – PUP trial 3908</u>

Seven (7) events within SOC 'nervous system disorders' and 2 events within SOC 'psychiatric disorders' were reported in PUPs in trial 3908. Of these, 5 events within SOC 'nervous system disorders' were reported as serious adverse events in 4 patients ('cerebral haemorrhage' [2 patients], 'febrile convulsions' and 'seizure'). One (1) event within the SOC 'psychiatric disorders' were reported as a serious adverse event ('delirium').

Five (5) serious adverse events within SOC 'nervous system disorders' and SOC 'psychiatric disorders' were reported:

- A toddler experienced 'cerebral haemorrhage' due to a fall after 3 EDs. The event was reported as unlikely related to N8-GP and recovered/resolved with sequelae by the investigator. However, due to a protocol violation of 'use of coagulation factors other than N8-GP or anticoagulants in relation

to ITI' the patient was discontinued from the trial. The event occurred while the patient was on pre-prophylaxis.

- This patient on prophylaxis treatment experienced 'cerebral haemorrhage' (severe in intensity) and 'seizure' (moderate in intensity) after 11 EDs and was admitted to the hospital. Prior to the event, the patient had developed FVIII inhibitor (low-titre inhibitor on ED 5) approximately 1 month earlier. Two (2) days after the event, the inhibitor test was repeated, and the results showed a high titre FVIII inhibitor of 36 BU/mL. The patient recovered from both the events (cerebral haemorrhage' and 'seizure) and was assessed as unlikely related to N8-GP by the investigator. Since, the development of FVIII inhibitor anti-bodies increases the risk of bleeds in patients with haemophilia, Novo Nordisk assessed that a causal relationship between the event of 'cerebral haemorrhage' and N8-GP treatment could not be ruled out. The N8-GP treatment was temporarily interrupted and re-introduced at increased dose.
- Another toddler patient on pre-prophylaxis experienced SAE of 'febrile convulsion' after 1 ED. The event was reported as mild in severity, unlikely related to N8-GP treatment and recovered/resolved by the investigator. The patient continued with N8-GP treatment.
- A very yound child on prophylaxis treatment reported a SAE of 'delirium' (SOC 'psychiatric disorders') after 293 EDs. The patient presented with 'delirium' induced by high grade fever as reported by the investigator and experienced hallucinations. The event 'delirium' was reported as recovered/resolved and unlikely related to N8-GP by the investigator. The patient continued with N8-GP treatment.

Rare events – PTP trials

No safety concerns were identified in the search of rare events. A total of 54 adverse events in 45 patients were identified in the search. The adverse events were reported across 10 SOCs and with no clustering. All events (by PT) were reported only once, except events of 'atrial fibrillation', 'ventricular extrasystoles', 'phimosis', 'gastric varices', 'neutropenia' (all reported with 2 events); 'gilbert's syndrome', 'hepatic fibrosis' and 'hepatic steatosis' (3 events) and 'thrombocytopenia' and 'palpitations' (4 events). One (1) of 54 adverse events was reported in a child (PT: 'swelling of eyelid'; non-serious, mild in severity, unlikely related to N8-GP by the investigator).

Rare events - PUP trial 3908

No safety concerns were identified in the search of rare events. A total of 12 adverse events in 12 patients were identified in the search. The adverse events were reported across 7 SOCs and with no clustering. All events (by PT) were reported only once, except for the event of 'bronchiolitis' (3 events).

Bridging of PEG-related clinical safety data available for N9-GP (Refixia) to N8-GP (Esperoct)

N9-GP, a PEGylated recombinant factor IX (rFIX) product was approved in 2017 for use in patients aged 12 years and above. Recently an extension of indication (EMEA/H/C/004178/II/0032) to include all age groups was approved in August 2023. N9-GP demonstrated favourable prophylactic and haemostatic efficacy and safety in clinical trials across all age groups, and furthermore, provided extensive clinical PEG safety data showing no safety concerns related to long-term exposure to PEG.

PEGylation

Both N8-GP and N9-GP consist of a 40 kDa PEG moiety which has shown to prolong the coagulation factor (FVIII or FIX) half-life. The PEGylated moiety for both the products cleaves-off upon activation, leaving the native activated factor (FVIIIa or FIXa). Upon its activation, the enzymatically and chemically stable PEG moiety is released intact back into the circulation, subsequently being excreted primarily via urine and in small amounts through faeces for both N8-GP and N9-GP, respectively.

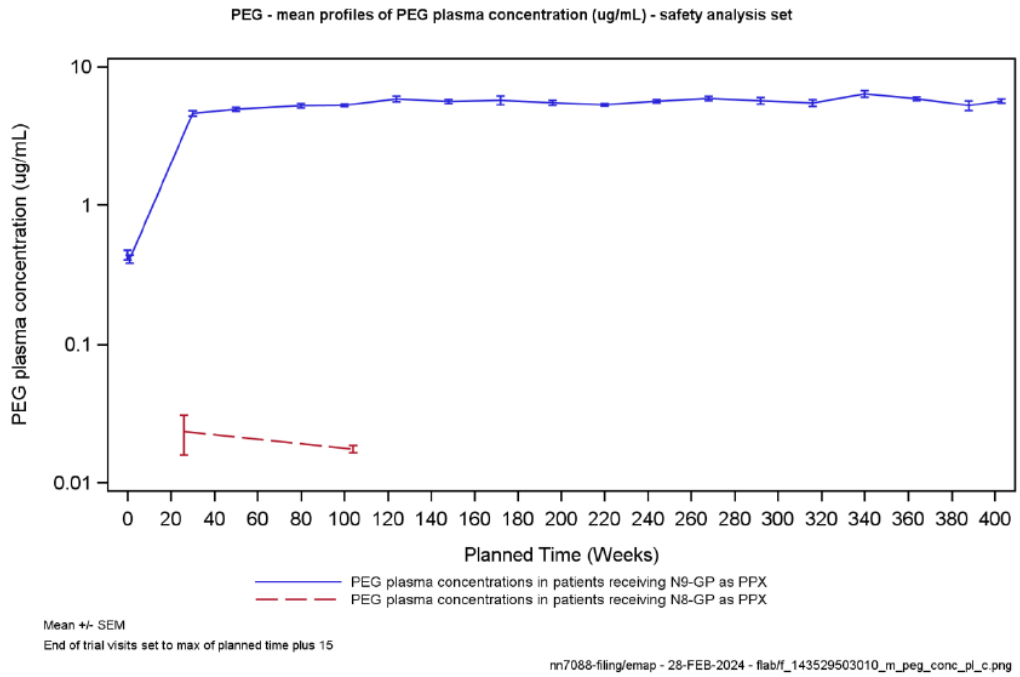
N8-GP

In the clinical trials conducted for N8-GP, PEG plasma concentrations in PTPs (children <12 years in trial 3885 and adolescent and adult in trial 3859) were analysed using LC-MS/MS. The PEG plasma concentrations were measured for periods of up to 5 years for children, adolescents and adults receiving N8-GP treatment. To assess the PEG concentration in the clinical trials for N8-GP, a semi-mechanistic plasma-tissue pharmacokinetic model was developed based on nonclinical rat distribution data for a single dose. The measured PEG concentrations were then compared with the predicted steady-state levels from this model. Detectable PEG concentrations ranged from 10.0 to 35.9 ng/mL in plasma in children and from 10.1 to 34.2 ng/mL in adults and adolescents. Although the dose in children was slightly higher than in adults (60 IU/kg twice weekly vs. 50 IU/kg Q4D), model-predicted steady-state PEG concentrations were similar in children and adults. This is likely due to the faster clearance rate in children.

N9-GP

In the paediatric trials 3774 (PTPs) and 3895 (PUPs) , routine measurements of PEG plasma concentration were conducted, both prospectively and retrospectively. This was done to confirm if the PEG steady-state concentrations in patients treated with N9-GP were well below the steady-state PEG concentration observed in the nonclinical toxicity studies. Additional historic visit samples were also included, if available, in this analysis. In both PTP trial 3774 and PUP trial 3895, the steady-state measurements of PEG plasma concentration were reached approximately 6 months after prophylaxis treatment initiation and remained so until last measurement on treatment (until EOT). The mean steady-state PEG plasma concentration was stable over time and ranged from 4.6 to 6.4 µg/mL during the trial. The PEG steady-state plasma concentrations were maintained for up to 6.5 years during continuous prophylaxis treatment with N9-GP confirming that once steady-state has been reached, the PEG plasma concentration remains stable and does not increase further.

Figure 17: Mean PEG plasma concentration versus time profile in N8-GP (PTP trial 4410) and N9-GP (PUP trial 3895) – safety analysis



Mean PEG plasma concentration (µg/ml) +/- SEM from N8-GP (red) and N9-GP (blue).

Data on PEG plasma concentration for N8-GP from Trial 4410 after patients have reached steady-state PEG plasma concentration (PTPs receiving prophylaxis with N8-GP). Data on PEG plasma concentration for N9-GP from Trial 3895 (PUPs receiving prophylaxis with N9-GP).

Abbreviations: PEG = polyethylene glycol; PPX = prophylaxis; SEM = standard error of the mean

The MAH has conducted evaluations of PEG safety through assessment of PEG plasma concentration, renal, hepatic and CNS-related AEs for both N8-GP and N9-GP and furthermore conducted extensive evaluation of neurodevelopment in children for N9-GP.

The conclusions from these assessments were:

- PEG plasma concentrations for both N8-GP and N9-GP reached steady-state on prophylaxis within 6 months and did not increase after the treatment had reached steady-state. Following discontinuation of therapy PEG plasma concentration decreased for both N8-GP and N9-GP.
- A few renal and hepatic AEs were observed and all patients recovered while on treatment, except 1 patient on N9-GP treatment. All these AEs were reported as unlikely related to the N8-GP and N9-GP treatment.
- There were no correlations observed between PEG plasma concentration and CNS-related AEs, and the CNS related AEs per PYE were similar in N8-GP [0.18 AEs per PYE] and N9-GP [0.2 AEs per PYE] for PTPs, respectively. The distribution of AEs with regards to severity was comparable between N8-GP and N9-GP, with the majority being assessed as mild or moderate. Two of the three CNS-related AEs were reported as possibly related to N8-GP by the investigator, all patients recovered while on treatment and Novo Nordisk assessed them to be unlikely related to N8-GP treatment.
- Extensive neurocognitive and neurological assessments were carried out for N9-GP to address potential impact on neurodevelopment in children in relation to long-term PEG exposure. An independent expert panel of paediatric neuropsychologists, neurologist and haematologist, evaluated key neurodevelopmental, neurocognitive, neurological and neurobehavioral milestones on an ongoing basis, both at trial and at individual level. There was no impact on any neurodevelopmental milestones. The children receiving N9-GP treatment had a performance comparable to a normative age-matched control group (eTHINK study).

Laboratory findings

Immunogenicity

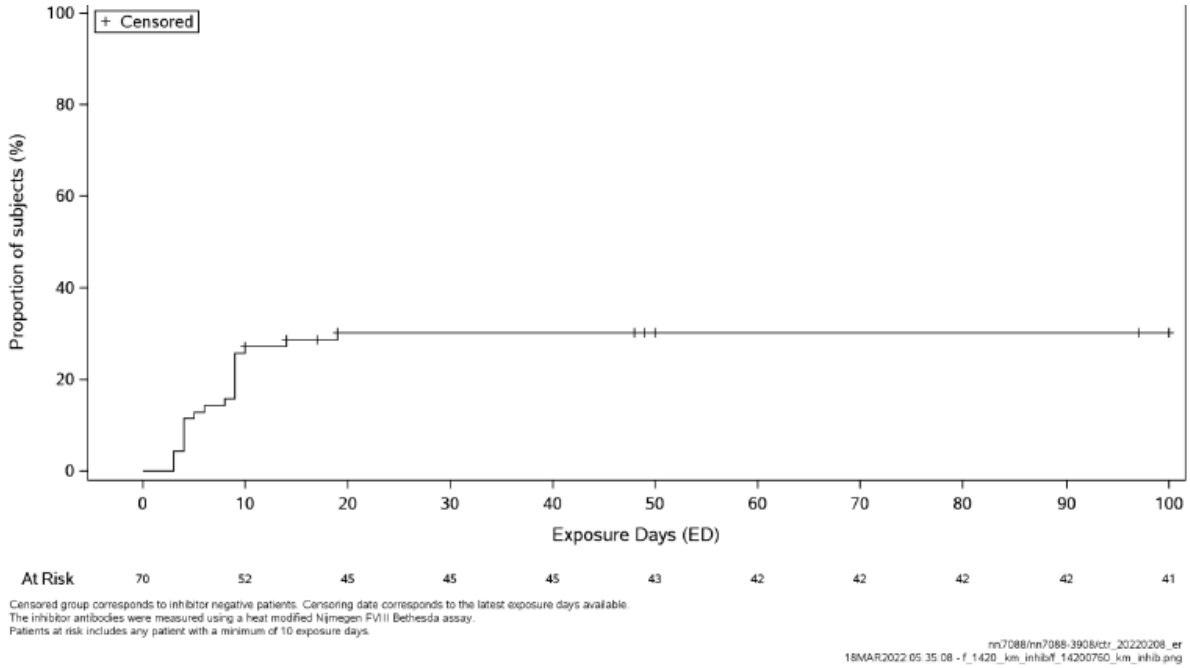
FVIII inhibitors - trials in PTPs

All patients were tested for FVIII inhibitors and all detections of FVIII inhibitors were recorded as adverse events and medical events of special interest. No confirmed FVIII inhibitors were reported in children in trials 3885 and 4410. One (1) event of confirmed 'FVIII inhibitors' was reported in an adult PTP (trial 3859).

FVIII inhibitors – PUP trial 3908

Inhibitor incidence was the primary endpoint in PUP trial 3908. Of the total 21 patients with confirmed FVIII inhibitors (≥0.6 BU), 11 patients were confirmed positive while receiving pre-prophylaxis and 10 patients were confirmed positive while receiving prophylaxis. The total estimated incidence rate of inhibitors (1-sided 97.5% upper confidence limit) was 0.300 (0.421) for all at risk patients (main + extension phase, at risk patients are patients dosed at least 10 times with N8-GP). High titre inhibitors are defined as inhibitors >5 BU. A total of 11 patients were confirmed with high titre inhibitors, of which 3 patients were confirmed while receiving pre-prophylaxis treatment and 8 patients were confirmed while receiving prophylaxis

Figure 18: Kaplan-Meier plot – time to positive inhibitors – main + extension – safety analysis set



Other ADAs

Assessments of non-neutralising anti-N8-GP antibodies and anti-PEG antibodies were done in all clinical trials. Assessments of anti-CHO HCP antibodies were performed in all trials in cases of a severe allergic/anaphylactic reaction. Furthermore, the protocols for trials 3859 and 3885 were amended to also include routine analysis of anti-CHO HCP antibodies using the blood samples drawn for anti-N8-GP antibodies, if the blood sample volume allowed. This was done in order to collect samples following the change in production facility and method of N8-GP drug substance.

Other ADAs in PTPs

Anti-N8-GP antibodies were identified in 6 patients (trials 3859 and 3885), of which 2 were positive for anti-FVIII antibodies prior to exposure to N8-GP. Of the remaining 4 patients; 1 was a child; all developed anti-N8-GP antibodies after dosing with N8-GP. One (1) of these patients was the FVIII inhibitor patient described in the inhibitor section above, and the other 3 patients were only transiently positive. The incremental recovery was only affected for 1 patient, and there were no relevant adverse events reported around the time of the positive results. Patients that underwent major surgery (trial 3860) were followed with close monitoring several months after surgery to assess potential development of inhibitors. None of these patients with intensified N8-GP therapy developed anti-N8-GP antibodies after the surgery.

In total, 37 patients from the global trials 3859, 4410 and 3885 had pre-existing *anti-PEG antibodies* of which the age group from 0–5 years had the highest frequency (48.5%).

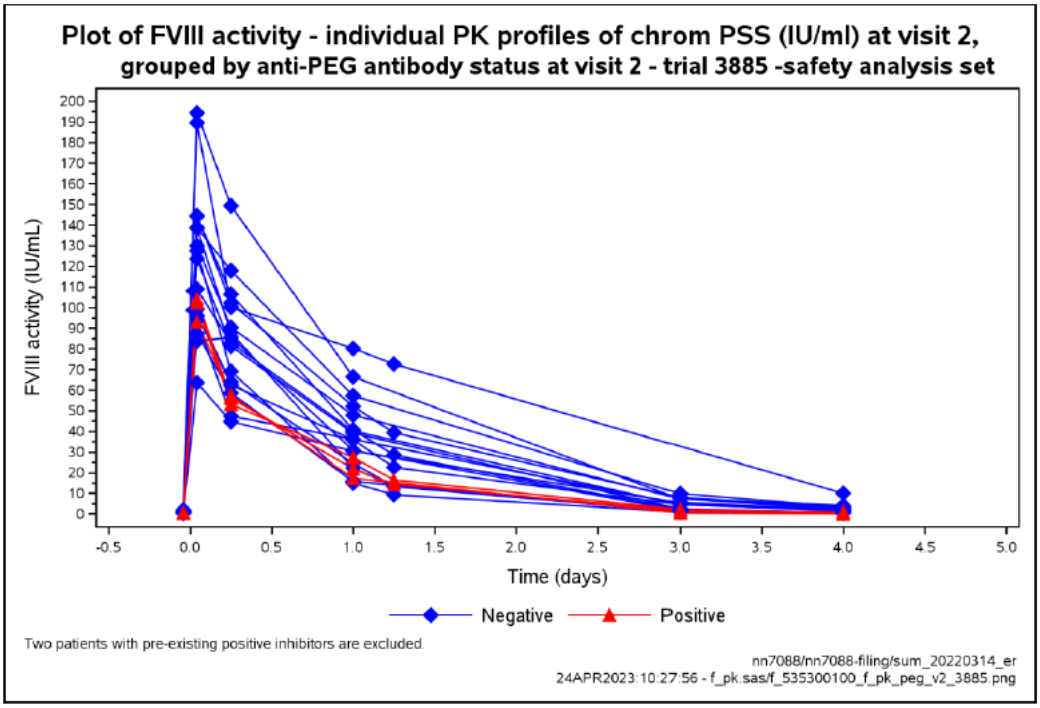
Figure 19: Pre-existing anti-PEG antibodies versus age – trials 3859 and 3885 – safety analysis set

Age group	Total number of patients N	Number of patients with pre-existing positive anti-PEG antibodies N(%)	Titre Mean(SD)	Titre Median	Titre [Min ; Max]
0-5 years	33	16(48.5)	1.3(1.2)	0.5	[0.5 ; 4.0]
6-11 years	34	4(11.8)	2.8(3.6)	1.3	[0.5 ; 8.0]
12-17 years	25	-	-	-	-
>=18 years	161	12(7.5)	19.2(13.1)	10.0	[10 ; 40]
Total	253	32(12.6)	8.2(11.7)	2.0	[0.5 ; 40]

N: Number of patients.
SD:Standard deviation.
Patients are allocated to age groups according to the age at baseline from the first trial.
Two patients with pre-existing positive inhibitors are excluded.
Some patients have been dosed 1 time with N8-GP in the phase 1 trial before entering phase 3 trials.
Minimum Required Dilution(MRD) was not multiplied to the shown titre. For anti-N8-GP antibodies the MRD was 7
for anti-PEG antibodies and the anti-CHO HCP antibodies the MRD was 10.

During the trial programme, 11 patients in trial 3859 and 1 patient in trial 3885 developed transient low-titre anti-PEG antibodies (negative – positive). One (1) of these patients were positive for anti-PEG antibodies only at the last visit. Twenty (20) of the 37 patients who had pre-existing anti-PEG antibodies did not have measurable anti-PEG antibodies post N8-GP administration. Out of the remaining 12 patients with pre-existing antibodies, 9 patients had post dose anti-PEG antibodies at one or more visits and 3 patients did not have any post dose measurements. For 6 patients where the anti-PEG antibody tests were negative or positive pre dose and missing post dose since the patients were withdrawn within one month after administration of N8-GP. 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 PK profiles between the patients who were anti-PEG antibody positive and those who were negativ). In addition, none of the patients who underwent major surgery with intensified N8-GP therapy developed anti-PEG antibodies after the surgery.

Figure 20: 10:Plot of FVIII activity – individual PK profile of chrom PSS (IU/ml) at visit 2, grouped by anti-PEG antibody status at visit 2 – trial 3885 – safety analysis set



Anti-CHO HCP antibodies were identified in 11 patients (trials 3859 and 3885), of which 2 were positive prior to exposure to N8-GP. Nine (9) patients; of which 3 were children, developed low-titre anti-CHO HCP antibodies after exposure to N8-GP. Of the 9 patients, 3 had persistent anti-CHO HCP antibodies. No relevant adverse events were reported around the time of the positive anti-CHO HCP antibody results. None of the patients who underwent major surgery developed anti-CHO HCP antibodies after the surgery (trial 3860).

Other ADAs in PUP trial 3908

Of a total of 81 exposed patients, 42 patients (51.9 %) developed anti-N8-GP binding antibodies, 22 patients (27.1%) developed anti-PEG IgM binding antibodies and 51 patients (63.0%) developed anti-PEG IgG binding antibodies. 21 patients were in the inhibitor group and 59 patients were in the non-inhibitor group. Of the 59 patients in the non-inhibitor group:

- 28 patients had no measurements of decreased incremental recovery (IR)
- 14 patients had only singles measurement(s) of decreased IR
- 17 patients had consecutive measurements of decreased IR low IR group (low IR group).

Inhibitor group (21 patients)

For Anti-N8-GP antibodies:

- At visit 1, 1 patient (6.3%) was positive for anti-N8-GP antibody with a titre value of 4.0. By visit 4, 20 patients (95.2%) were positive for the antibody with a median titre value of 64.0. The number of anti-N8-GP positive patients showed a steady decrease after visit 4 and 6 patients (42.9%) of the remaining 14 patients at EOT were positive for the antibody with median titre value of 136.
- For anti-PEG IgM antibodies:

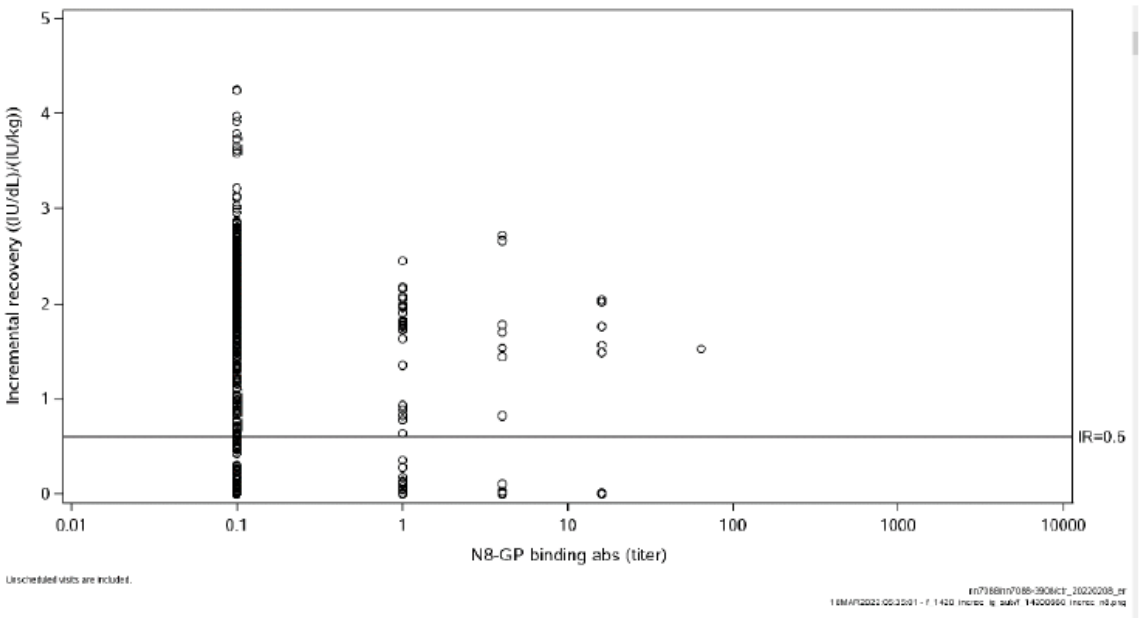
- At visit 1, 6 patients (35.3%) were positive for anti-PEG IgM antibodies with a median titre value of 1.5. By visit 3 (approximately 4 EDs), 8 patients (50%) were positive for the antibody with a median titre value of 4.0. The titre value decreased with each visit post visit 3 and at EOT only 2 patients (13.3%) were positive for anti-PEG IgM antibody with a median titre value of 1.5.
- For Anti-PEG IgG
- At visit 1, 5 patients (31.3%) were positive for anti-PEG IgG antibodies with a median titre value of 1.5. By visit 4, 15 patients (75%) were positive for the antibody with a median titre value of 64.0. At EOT, 5 patients (33.3%) with a median titre value of 4.0 were positive for the antibody.

Temporarily Decreased IR group (17 patients)

For Anti-N8-GP antibodies:

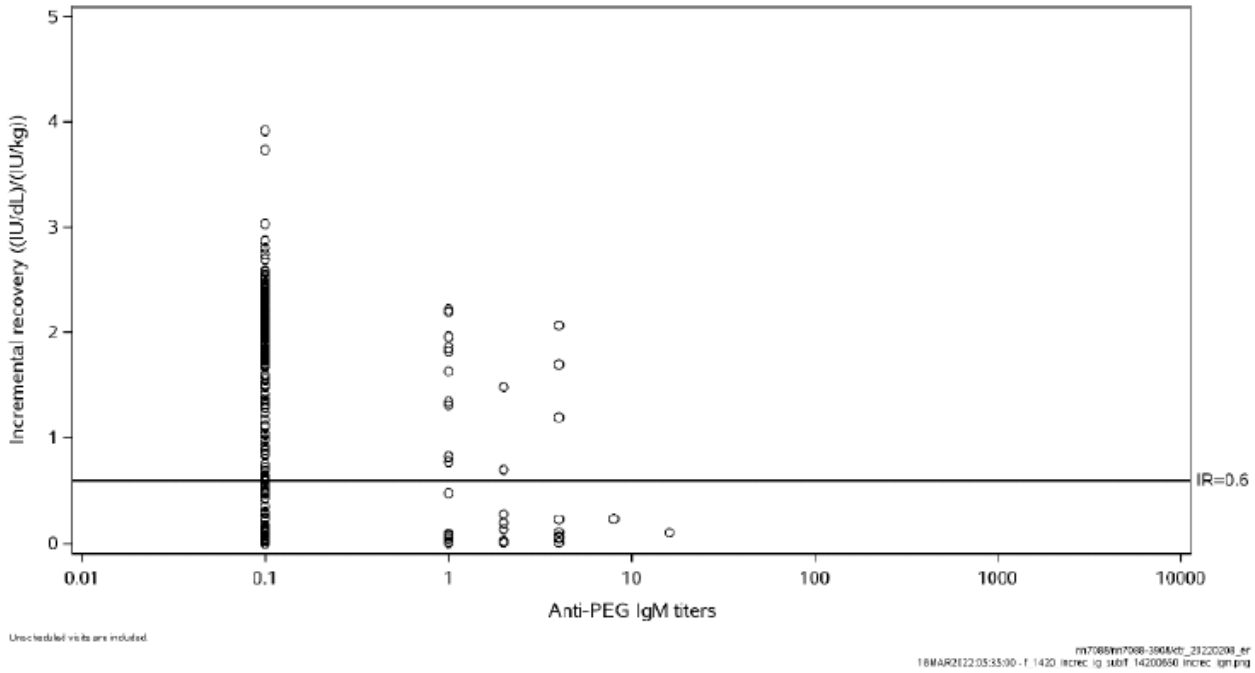
- At visit 1 (baseline), none of the patients presented with positive anti-N8-GP antibodies. However, by visit 3 sseven (41.2%) patient had a positive anti-N8-GP antibodies with a median titre value of 1.0. At EOT, there were 4 patients (26.7%) with positive anti-N8-GP antibody with a median titre value of 4.0. 11 of 17 patients (64.7%) developed anti-N8-GP binding antibodies during the trial.
- For anti-PEG IgM antibodies:
- At visit 1, 4 patients (30.8%) presented with positive antibodies with a median titre value of 1.0. and by visit 3, 12 patients (70.6%) were positive for the antibody with a median titre value of 2.0. At EOT, only 1 patient (6.7%) was anti-PEG IgM positive with a low titre value of 2.0.
- For anti-PEG IgG antibodies:
- At visit 1, 4 patients (28.6%) presented with positive antibodies. All 16 patients (100%) screened at the next visit (visit 3) were positive for anti-PEG IgG antibody with a median titre value of 128.0. As compared to anti-N8 GP antibody and anti-PEG IgM, anti-PEG IgG positive patients' titres decreased more slowly over time. At EOT the median titre value was 3.0, seen in 10 patients (71.4%) positive for the antibody.

Figure 21: Plot of incremental recovery vs anti N8-GP Ab titer – non inhibitor patients safety analysis set



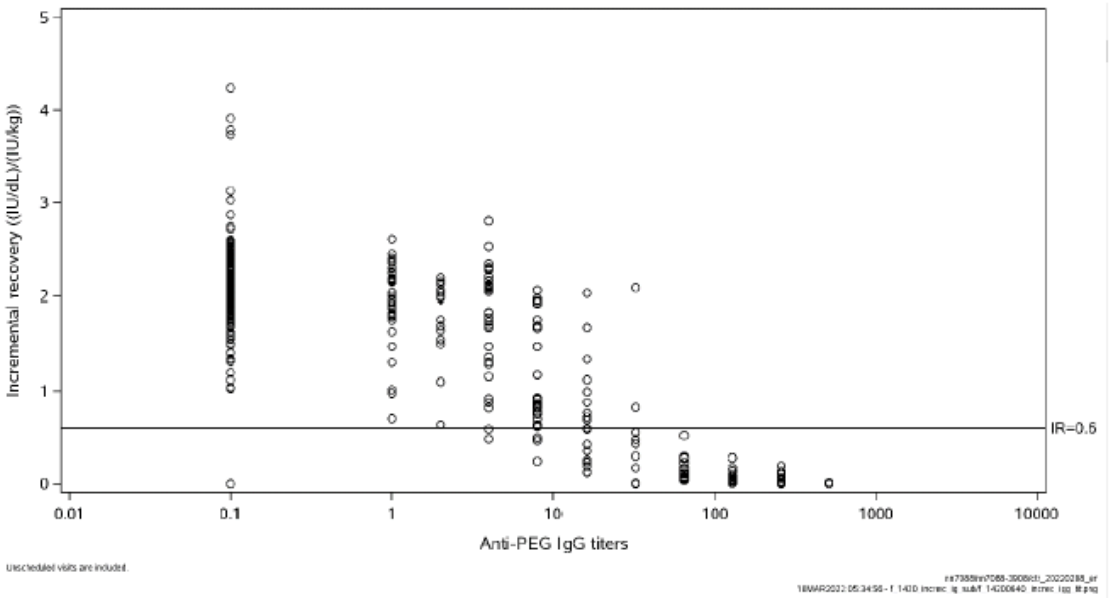
Cross-reference: Trial 3908 (M 5.3.5.2), Figure 11-6

Figure 22: Plot of incremental recovery vs anti PEG IgM Ab titer – non-inhibitor patients – safety analysis set



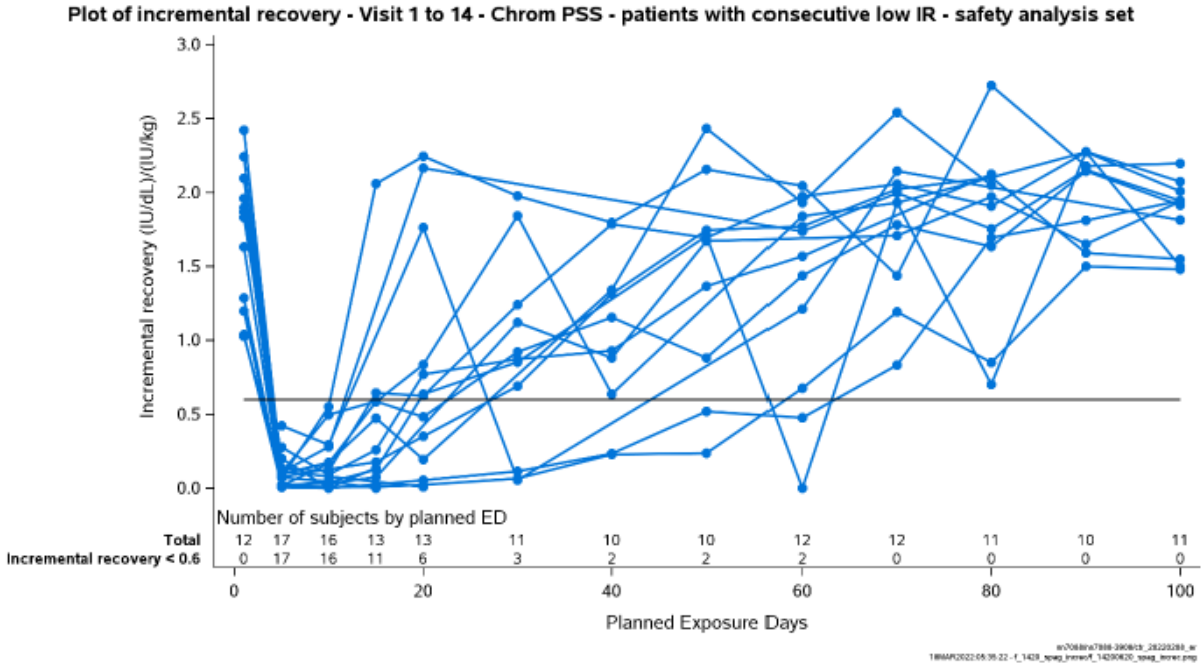
Cross-reference: Trial 3908 (M 5.3.5.2), Figure 11-7

Figure 23: Plot of incremental recovery vs anti PEG IgG titer – non-inhibitor patients – safety analysis set



Cross-reference: Trial 3908 [M 5.3.5.2] Figure 11-8

Figure 24: Individual profiles of IR – visits 1 to 14- Chrom PSS- non-inhibitor patients with consecutive decreased IR – safety analysis set



The 13 measurement timepoints correspond to visit 1 (1 ED), visit 3 (5 EDs), visit 4 (10 EDs), visit 5 (15 EDs), visit 6 (20 EDs), visit 7 (30 EDs), visit 8 (40 EDs), visit 9 (50 EDs), visit 10 (60 EDs), visit 11 (70 EDs), visit 12 (80 EDs), visit 13 (90 EDs), visit 14 (100 EDs).

Non-inhibitor and non-low IR group (42 patients)

For Anti-N8-GP antibodies:

- There was no significant increase in the number of patients positive for anti-N8-GP antibodies by visit. The highest number of patients positive for the antibody was seen in visit 5 (4 patients [13.3%]) with a median titre value of 1.0. Eleven of 42 patients (26.2%) developed anti-N8-GP binding antibodies during the trial.
- For anti-PEG IgM antibodies:
- At visit 1, 6 patients (17.6%) presented with anti-PEG IgM antibodies with a median titre valueof 2.0. The number of patients with anti-PEG IgM antibodies remained low for the rest of the visits and at EOT 3 antibody positive patients (8.1%) were recorded.
- For anti-PEG IgG antibodies:
- At visit 1, 4 patients (12.1%) patients were positive for anti-PEG IgG antibodies. At visit 3 and visit 4, 19 patients (63.3%) presented with antibodies with a median titre value of 16 and 4, respectively. In comparison, the anti-N8-GP antibody and anti-PEG IgM antibody, anti-PEG IgG antibody titres remained high in the non-inhibitor non-low IR group for longer and at EOT 6 patients (19%) of the remaining 32 patients remained.

Anti-CHO HCP antibodies

HCP are small pieces of protein remaining from the synthesis of recombinant FVIII in CHO cells. Small amounts of this protein may be present in the drug product if they are not removed during the purification process and could potentially elicit an immune response.

The analysis of HCP antibodies included the following time points: samples collected pre-dose prior to first N8-GP exposure and every 6 months until visit 9 and every 12 months post that.

In the inhibitor group, one (1) patient was anti-CHO HCP positive at visit 1 with a median titre value of 27. In the low IR group, a total of 2 patients were positive and remained positive till EOT (median titre value of 9 at EOT). In non-inhibitor non low IR group, a total of 3 patients were positive with low titre values and were negative at EOT.

Comparison of immunogenicity between N8-GP from the pivotal process and N8-GP from the commercial process (PTPs)

As of the data cut-off date, 184 out of 254 patients were switched from the pivotal process to the commercial process. In the following, only patients that had been tested for anti-drug antibodies were included. None of the 121 tested patients from trial 3859 that were switched from pivotal process and exposed to trial product from the commercial process developed FVIII inhibitors or anti-N8-GP antibodies. Likewise, none of the 63 patients from trial 3885 switched from pivotal process and were exposed to trial product from the commercial process developed FVIII inhibitors or anti-N8-GP antibodies, respectively. The patients were tested in average 5.49 and 5.48 times, respectively, with approximately 3 to 6 months between the tests when switched to the commercial process.

The tests for anti-PEG antibodies were done less frequent than the tests for the FVIII inhibitor. The test results were available for 120 patients in trial 3859 and for 63 patients in trial 3885 following switch from the pivotal process to the commercial process. In total, 7 patients were positive for anti-PEG antibodies following switch to the commercial process indicating no increase in PEG immunogenicity for N8-GP from the commercial process. The average testing rate for anti-PEG antibodies was 2.40 times.

Anti-CHO HCP antibody tests were also performed less frequent than for FVIII inhibitors and anti-N8-GP antibodies. Anti-CHO HCP antibodies were tested in 121 patients in trial 3859 and in 63 patients in trial 3885 following switch from pivotal to commercial process. Six (6) patients from the commercial process were found positive for anti-CHO HCP antibodies after the switch. Two patients were positive prior to the switch with no increase in titre and two patients developed antibodies with titre 1 (10 including MRD) after the switch. The last patient was transient positive during dosing with N8-GP from both the pivotal and commercial process.

As only 6 patients developed anti-CHO HCP antibodies following switch to the commercial process this indicates no increase in CHO HCP immunogenicity for N8-GP from the commercial process.

Clinical laboratory adverse events

All clinically significant changes in laboratory tests were to be reported as adverse events and are included in the summary of all adverse events under the SOCs ‘investigations' and ‘blood and lymphatic system disorders’ and are therefore included in the overall analysis of adverse events

Haematology

Standard haematology parameters were assessed in all the clinical trials. No clinically relevant abnormalities were apparent in any of the trials.

In the surgery trial 3860, there was an expected post-operative decrease in mean RBC count, haemoglobin and haematocrit and an increase in platelets at end-of-trial compared to baseline. There were also variations in other haematology parameters during and after surgery; these were expected and had generally returned to baseline at the end-of-trial.

Biochemistry

Standard biochemistry parameters were assessed in all the clinical trials. Overall, no clinically relevant changes associated with exposure to N8-GP have been observed for biochemistry parameters. The observed abnormalities were as expected for the patient population.

Assessment of hepatic and renal laboratory parameters had special attention in the safety assessment of N8-GP and are discussed in the section on AESIs.

In the surgery trial 3860 there were, as expected, some post-operative variations in the biochemistry parameters; these had generally returned to baseline-values at the end-of-trial.

Coagulation-related parameters

Coagulation-related parameters were assessed in all trials, except trials 3885 and 4033.

As expected, a decrease in aPTT was observed after N8-GP administration in all trials. No other clinically relevant changes were observed in coagulation-related parameters.

Urinalysis

Urinalysis was performed in trial 3776 and 4410; no clinically relevant changes in any of the urinalysis parameters were observed.

PEG plasma concentration

The PEG plasma concentration levels were analysed in non-clinical and clinical studies in the N8-GP development program. In the non-clinical program, immunohistochemistry staining of the brain tissue to assess PEG distribution was performed during a chronic repeat-dose toxicity study in Rowett nude rats. In this study, no treatment-related histopathological changes or concerns due to long term safety were seen in any organs and PEG was not detected in any brain tissues (including the choroid plexus). PEG plasma levels were measured in the 52-weeks repeat dose toxicity study in rat by NMR and plasma was reanalysed by a more sensitive HPLC-MS/MS method. The steady-state PEG plasma concentration after 52 weeks of repeated dosing of 1200 IU/kg every 4th day was 85.1 ± 17.8 ng/mL (see Table 59). Steady-state plasma PEG levels were predicted to have been reached within the first 1.5 months in rats and decreased markedly within 2 weeks following N8-GP treatment cessation, suggesting that PEG is removed relatively rapidly from plasma once treatment ceases. Furthermore, in CSF samples taken at terminal kill after 52 weeks of dosing and the 2 week recovery, PEG was not measurable by HPLC-MS/MS.

In the clinical studies, PEG concentration levels were measured in previously treated children (trial 3885) and in adolescent and adult PTPs (trial 3859) and analysed using LC–MS/MS.35 Steady-state plasma PEG levels were predicted to have been reached within 6 months in both patient populations. Human plasma PEG levels were several folds lower (five- to eight-fold) than those reported at the no-observed adverse-effect-level in the 52-week rat toxicity study (Figure 25). PEG exposure in children was slightly higher than that in adolescents and adults, which is likely due to the higher N8-GP (and therefore PEG) dose as well as the shorter dose interval.

The plasma steady state exposure ratios from the 52-weeks chronic toxicity study in Rowett nude rats to steady state PEG plasma exposure in previously treated adults and children exposed to N8-GP for 2-5 years is presented in Table 59.

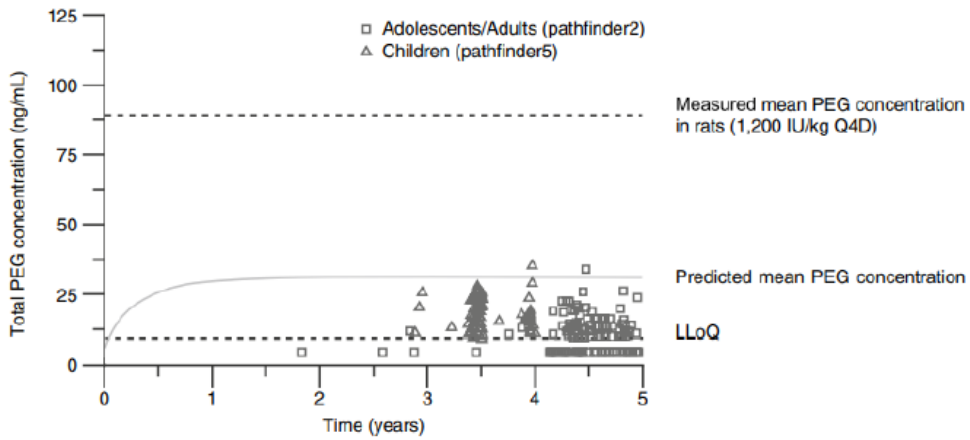
Table 59: PEG plasma exposure ratios rat/human at steady state

Species	Dose	Treatment duration at sampling	PEG exposure mean ± SD[1] (ng/mL)	Plasma PEG exposure ratio (rat/human)
Rat - males	1200 IU/kg/4th day	52-weeks	85.1 ± 17.8 (N=16)[2]	-
Human (≥12 years of age)	50 IU/kg/4th day	2–5 years	10.7 ± 5.5[3]	8.0
Human (<12 year of age)	60 IU/kg/twice weekly	2–5 years	18.5 ± 6.9[3]	4.6

Data from Bjørnsdottir et al. 2020[35]. [1]To calculate means plasma samples below Lower limit of quantification (LLoQ) was set to half LLoQ. [2]LLoQ in rat plasma was 13 ng/mL, [3]LLoQ in human plasma was 10 ng/mL.
Abbreviations: PEG = polyethylene glycol; SD: standard deviation.

Clinically, a twice weekly dose of 50 IU/kg will result in PEG exposure/dose that is more than 1300-fold lower than the threshold of 0.4 µmol/kg/month dose, where ependymal cell vacuolation has been observed in nonclinical models.

Figure 25: Predicted and measured PEG concentrations in children, adolescents and adults measured after 2-5 years of exposure to N8-GP



Data from Bjørnsdottir et al. 2020[35].Children (pathfnder5) were treated with 60 IU/kg N8-GP twice weekly (open triangles). Adolescents and adults (pathfnder2) were treated with 50 IU/kg N8-GP Q4D (open squares). Mean PEG exposure during the 52-week rat toxicity study is indicated by the upper dotted line, and the LLoQ is shown by the lower dotted line. Predicted mean PEG exposure in children, adolescents and adults (grey solid line) is shown as a reference. The mean measured plasma PEG concentration for children, adolescents and adults was 13.3 ng/mL.
Abbreviations: LLoQ = lower limit of quantifcation; N8-GP = turoctocog alfa pegol; PEG = polyethylene glycol; Q4D = every 4th day

Safety related to drug-drug interactions and other interactions

No drug interaction studies have been performed. Formal drug-drug interaction studies are generally not applicable for coagulation factors.

Discontinuation due to adverse events

Adverse events leading to withdrawal - PTPs

Five (5) patients (≥12 years of age) were withdrawn from trial 3859 and 2 patients (<12 years of age) were withdrawn from trial 3885 due to adverse events; see Table 60. In addition, 2 patients were withdrawn because they met a withdrawal criterion related to safety; 1 patient in trial 3859 was withdrawn because he met the withdrawal criterion 'FVIII inhibitor' (>5 BU) as confirmed by re-testing by the central laboratory and 1 child in trial 3885 was withdrawn because he met the withdrawal criterion 'allergy/anaphylaxis related to trial product'. Both patients are therefore also included in Table 60 even though the reason for withdrawal was not stated as due to an adverse event.

Six (6) of the 7 adverse events leading to withdrawal were serious adverse events. One (1) adverse event (haemorrhage; trial 3885) was judged by the investigator to be probably related to N8-GP, while the remaining events were judged to be unlikely related to N8-GP. Furthermore, for the 2 patients who were withdrawn due to withdrawal criteria related to safety, the adverse events were judged by the investigator to be probably related to N8-GP administration: 'FVIII inhibition' and 'hypersensitivity'.

No patients were withdrawn from trial 4410 due to adverse events.

Table 60: Adverse events leading to withdrawal – trials 3776, 3859, 4033, 3885, and 4410

Patient ID/ Trial	Age	Preferred term	ED	Relationship[a]	Severity	Serious	Outcome
	[redacted]	Pancreatic carcinoma metastatic	88	Unlikely	Moderate	Yes	Fatal
	[redacted]	Hepatocellular carcinoma	135	Unlikely	Moderate	Yes	Not recovered
	[redacted]	Duodenal ulcer	94	Unlikely	Severe	Yes	Recovered
	[redacted]	Road traffic accident	150	Unlikely	Moderate	Yes	Recovered
	[redacted]	Ankle fracture	156	Unlikely	Severe	Yes	Recovered
	[redacted]	Factor VIII inhibition	97	Probable	Moderate	Yes	Not recovered
	[redacted]	Haemorrhage	4	Probable	Moderate	Yes	Recovered
	[redacted]	Joint swelling	8	Unlikely	Mild	No	Recovered
	[redacted]	Hypersensitivity	4	Probable	Severe	Yes	Recovered

[a] The relationship to N8-GP as judged by the investigator.

[b] Both patients were withdrawn as they met a withdrawal criterion related to safety; thus, both patients are included in the table even though the reason for withdrawal was not stated as due to an adverse event. Patient ID [redacted] also had other adverse events (non-serious) related to allergic reactions; see Appendix 7.1, Listing 66.

Abbreviation: ED = exposure day

Adverse events leading to withdrawal – PUP trial 3908

Eight patients withrew due to an adverse event, all during the main part of the trial.

Table 61: Adverse events leading to withdrawal – trial 3908

Patient ID	Age (months)	Preferred term	ED	Relationship[a]	Severity	Serious	Outcome
		Drug hypersensitivity	259	Probable	Severe	No	Not recovered

[a] The relationship to N8-GP as judged by the investigator.

Abbreviation: ED = exposure day

Patient ID	Age (months at baseline)	Preferred term	Number of EDs at the occurrence of AE	Relationship	Severity	Serious	Outcome	Number of days since first dose of N8-GP till occurrence of AE
	[redacted]	Factor VIII inhibition	11	Probable	Severe	Yes	Recovered	679
	[redacted]	Vaccination site haemorrhage	5	Probable	Severe	Yes	Recovered with sequelae	134
	[redacted]	Anti-factor VIII antibody positive	5	Probable	Severe	Yes	Not recovered	18
	[redacted]	Anti-factor VIII antibody positive	2	Probable	Severe	No	Recovered	282
	[redacted]	Heart rate increased	3	Possible	Severe	Yes	Recovered	29
	[redacted]	Factor VIII inhibition	6	Possible	Severe	Yes	Not recovered	211
	[redacted]	Factor VIII inhibition	13	Probable	Moderate	Yes	Not recovered	127
	[redacted]	Factor VIII inhibition	16	Probable	Severe	Yes	Recovered	70

Cross-reference: Trial 3908-Full (M 5.3.5.2), Appendix 16.2.1, Listing 16.2.1.2; Trial 3908-Full (M 5.3.5.2), Table 14.3.1.20

Patient ID	Age (months)	Preferred term	ED	Relationship[a]	Severity	Serious	Outcome
		Drug hypersensitivity	259	Probable	Severe	No	Not recovered

[a] The relationship to N8-GP as judged by the investigator.

Abbreviation: ED = exposure day

Post marketing experience

The first marketing authorisation for N8-GP was received in the US on 19 February 2019. In the EU, a marketing authorisation was received on 20 June 2019. As of the cut-off date of 19 December 2022, N8-GP has been approved in more than 40 countries (Table 62).

Table 62: Approval and marketing status of N8-GP

Product (N8-GP)	Number of countries	Major regions and countries
Approved	>40	United States (US), European Union (EU), United Kingdom (UK), Norway, Iceland, Canada, Japan, Switzerland, Saudi Arabia, North Macedonia, Argentina, India, Serbia, Taiwan, United Arab Emirates, Turkey, Lebanon, Brazil, Colombia
Marketed	>20	Denmark, Austria, Bulgaria, Germany, Switzerland, The Netherlands, Czech Republic, Croatia, Norway, Sweden, Slovenia, Japan, Spain, Estonia, Italy, Portugal, United Kingdom, USA, Argentina, Belgium, Finland, Greece, India, and Luxembourg

In all regions, N8-GP is indicated for the treatment of bleeding episodes, prevention of bleeding in association with surgery and prophylaxis of bleeding episodes. The regional differences in the approved indications are presented in Table 63.

Table 63: Overview of regional differences in approved indications

Indication	EU	US	Switzerland	Canada	Japan
On-demand treatment	≥12 years	All ages	All ages	All ages	All ages
Prophylaxis					
Perioperative management					

The estimated global market exposure is shown in Table 63.

Table 64: Market exposure by operational region

	Patient-years of exposure (PYE)[a]					
	Europe[b]	China	Japan	US	Rest of the World	Total
Cumulative period	1,527	1	74	160	93	**1,855**

Note: Data are based on sales figures, including the volume of products released from Novo Nordisk as samples. As the exposure is based on volume distributed to external customers and average daily usage rather than actual patient exposure, the numbers can be over or underestimated.

Cumulative period refers to the period since the product was first marketed (01 August 2019) until December 2022. The distribution data of N8-GP reflected in the table is till Jun 2022 as the database allows retrieval with the input of month and year only.

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

[b]Europe includes the EEA, Switzerland and the UK.

Abbreviations: DDD = defined daily dose; EEA = European Economic Area; PYE = patient-years of exposure.

As part of **post-approval pharmacovigilance activities**, the MAH has monitored adverse events from all available sources (spontaneous and solicited) including

- spontaneously reported ARs
- events from market research programmes and patient support programmes
- Adverse events reported during the ongoing PASS NN7088-4029 and PASS NN7088-4484.

Adverse events reported in PASS NN7088-4029 and NN7088-4484 are included in this section.

As of 19 December 20226, 345 adverse events have been reported from post marketing sources of which 58 events were serious. Most frequently reported serious adverse events by PT were 'coagulation factor VIII level decreased' and 'drug specific antibody present'.

Inhibitor development

The narrow NNMQ search of 'antibody FVIII' identified 12 events among the 345 adverse events reported from post marketing- sources. Of the 12 events reported, 3 events (from 3 patients) were related to positive inhibitor titres. None of these were confirmed FVIII inhibitors as subsequent assays showed negative titres.

Allergic/hypersensitivity reactions

The narrow NNMQ search 'allergic reactions' identified 14 events among the 345 adverse events reported from post-marketing sources.

Thromboembolic events

The narrow SMQ search "thromboembolic events" identified 3 events in 3 cases among the 313 adverse events reported from post-marketing sources (Table 65).

Table 65: Thromboembolic events from post-marketing sources based on SMQ search

Preferred term	Non-serious	Serious
Atrial thrombosis	0	1
Myocardial infarction	0	1
Transient ischaemic attack	0	1

Anti-PEG antibodies

Decreased FVIII in PUPs

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

Decreased FVIII in PTPs

Cumulatively, 52 adverse events (from 35 valid cases) associated with anti-PEG antibodies and/or lack of drug effect have been identified from post-marketing sources with N8-GP as the suspected drug.

More than 70% of the adverse events captured from post-marketing sources were reported as non-serious and most cases had limited information available (despite requesting follow-up information for these cases). Some patients (8) had a confirmed medication or vaccination history with pegylated products such as COVID-19 vaccine.

From post-marketing reporting, occurrence of anti-PEG-antibodies has also been observed at time of switching to N8-GP. A comprehensive search was conducted to capture all events related to anti-PEG antibodies in PTPs. As of 19 December 2022, 35 validated cases have been reported which possibly could be related to the occurrence of anti-PEG antibodies. 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 8 cases were analysed centrally and identified to be positive for anti-PEG antibodies. Of the 8 analysed cases, 6 patients showed an anti-PEG antibody titre of clinical relevance (around titer 16). Clinical relevance was based on the titre results obtained from post-hoc analyses conducted in the PUP trial36 (trial 3908). The results suggested that for some of the post marketing cases involvement of anti-PEG antibodies might have led to the observed decrease in FVIII activity. Novo Nordisk concluded that the wide variation in clinical presentation does not provide a solid conclusion to a single underlying mechanism.

In the post-marketing setting, the frequency of PTPs with haemophilia A to develop the anti-PEG antibodies whilst on treatment with N8-GP or have high titer pre-existing anti-PEG antibodies is currently unknown. Detailed evaluation of available information does not change the current knowledge of the safety profile of N8-GP.

EU PASS (Study 4029)

Study 4029 is an ongoing non-interventional PASS conducted at the request of European Medicines Agency (EMA). The primary objective of the study is to investigate the safety of N8-GP including the PEG moiety during prophylaxis and treatment of bleeding episodes during long-term routine use in patients with haemophilia A. This study was initiated in October 2020 and 71 patients have been enrolled in the trial by 03 June 2022.

As of 19 December 2022, 25 adverse events have been reported in this study, of which 4 were serious adverse events. No specific clustering or pattern with regard to any specific PT was observed.

Japan post-marketing surveillance study (Study 4484)

Study 4484 is an ongoing non-interventional PMS study in Japan. The primary objective of the study is to assess the safety of N8-GP during long-term routine use in patients with haemophilia A.

This study was initiated in March 2021 and 9 patients have been enrolled in the trial as of date and recruitment is ongoing.

As of 19 December 2022, 10 adverse events have been reported in this study, of which none were serious adverse events. No safety concerns were identified.

EUHASS (Study 4557)

Study 4557 is an ongoing NIS with primary objective to investigate the safety of long-term exposure to N8-GP. The study includes all patients treated with N8-GP who report adverse events to the European Haemophilia Safety Surveillance System (EUHASS).

Data collection started in December 2020 and is planned to continue until April 2025. Data on adverse events related to N8-GP are reported from the registries to Novo Nordisk via annual reports. The EUHASS pharmacovigilance programme (http://web.euhass.org/) has monitored the safety of treatments for people with inherited bleeding disorders in Europe since October 2008.

According to the latest annual EUHASS report, covering the period from 01 October 2008 until 31 December 2021, one patient with non-severe haemophilia A of the N8-GP-treated patients in the EUHASS database has reported inhibitors. No allergic reactions or other acute reactions have been reported, i.e., no safety concerns have been identified.

2.5.1. Discussion on clinical safety

Turoctocog alfa pegol is licensed in the EU since 2019 for the treatment and prophylaxis of bleeding in patients with haemophilia A aged 12 years and above.

At the time of authorisation, published data from long-term nonclinical studies with other PEGylated proteins have shown vacuolation in macrophages and in cells of excretory organs like the kidney, liver and choroid plexus. Potential accumulation of the 40kD PEG-moiety in the nervous system tissue or other human tissue/organs as well as any potential clinical impact, such as on brain development in children e.g. on cognitive, functional or metabolic properties, remained an unknown risk of Esperoct when used for long-term treatment. Therefore, the indication of Esperoct was limited to adults and adolescents twelve years and above in whom most neurodevelopmental milestones are already reached.

To support the extension of the indication to children <12 years of age, the MAH has provided the following additional data:

- Trial 3885 – a phase 3 trial in previously treated children <12 years of age (main + extension phase). During the initial submission data from the main phase was submitted and in the current application results of final analysed data from main + extension phase are included.
- Trial 39082 – a phase 3a trial in previously untreated children <6 years of age. An interim report was submitted during the initial submission, while the current application includes the final analysed data from the complete trial.
- Trial 3859 – a phase 3 trial in adolescent and adult PTPs ≥12 years of age (main + two extension phases). An interim report was submitted during the initial submission, while the current application includes the final analysed data from the complete trial.
- Trial 3860 – a phase 3 surgery trial in PTPs ≥12 years of age. During the initial submission an interim report was submitted and in the current application results of final analysed data are included.
- Trial 4410 – a phase 3b long-term efficacy and safety trial in previously treated patients (PTPs) of all age groups. This trial was initiated after submission of the initial MAA application and completed post approval in the EU. Additional data on long-term safety and efficacy of N8-GP was obtained by recruiting patients from previous trials 3859 and 3885.
- Trial 4595 – phase 3b trial in adolescent and adult Chinese PTPs (≥12 years). Data from this trial is not pooled with the other ≥12 years PTPs since the trial was conducted in a cohort of Chinese adolescent and adult patients post initial MAA approval in the EU. Data from this trial is included only in PK and safety sections to support relevant results.

In addition, the MAH has provided a justification for the bridging to the safety data accrued with nonacog beta pegol (Refixia), a coagulation factor IX glycopegylated with the same 40kD PEG moiety as turoctocog alfa pegol and licensed since 2017 in the EU. The safety data for Refixia encompass the following:

- Trial 3774 ongoing extension phase – phase 3 trial in PTPs ≤12 years
- Trial 3895 ongoing main and extension phases – phase 3 trial in PUP) <6 years
- Study 4031 ongoing - global PASS in previously treated children, adolescents and adult patients
- Study 4404 ongoing - post-marketing surveillance (PMS) study in previously treated children, adolescents and adult patients in Japan.

Apart from the new trials/studies/exposure included in this submission as described above, additional safety assessments have been performed. These safety assessments comprise the following:

- PEG plasma concentration (in Trials 3747, 3775, 3774 and 3895).
- Neurological examination (NE) (in Trials 3774 and 3895).
- Neurocognitive assessments (NCAs) (in Trials 3774 and 3895).

- Collection of all CNS-related AEs and renal AEs as MESIs (in Trials 3774 and 3895)
- Determination of eGFR as a renal biomarker (in Trials 3774 and 3895).

Exposure

In the clinical development programme of N8-GP, overall 68 unique previously treated children have been exposed to N8-GP in the clinical trials 3885 and 4410 for a total of 43,698 EDs, corresponding to a total of 414.9 PYE; younger children (0-5 years) had a total of 19,759 EDs, corresponding to a total of 188.6 PYE and older children (6-11 years) had a total of 23,939 EDs, corresponding to a total of 226.3 PYE across trials. Of the total 68 unique previously treated children, 59 were exposed for more than 5 years, 55 were exposed for more than 6 years and 21 children for more than 7 years.

In PUP trial 3908, a total of 81 patients (including main phase + extension phase + ITI treatment) were exposed for 18,184 EDs corresponding to a total of 233.8 PYE. Excluding the ITI treatment, the 81 patients were exposed to 16,670 EDs corresponding to a total of 224.3 PYE.

Adverse Events

AE incidence

PTPs: In study 8885 in a paediatric PTPs a total of 66 patients reported a total of 838 AEs. The most frequent AEs were upper respiratory tract infection (51 events), nasopharyngitis (37 events), cough (32 events), epistaxis (31events), pyrexia (26 events) and gastroenteritis (23 events).

In the adolescent patients (12–17 years), the rate of adverse events per PYE was slightly higher than in children (0-5 years and 6-11 years) and adults (≥18 years): 3.07 versus 2.96 (0–5 years), 2.38 (6-11 years) and 2.04 (≥18 years). However, the overall adverse event pattern in adolescents did not raise any safety concern; this age group did not have higher rates of serious adverse events, severe adverse events or events judged as possibly or probably related to N8-GP administration compared to the other age groups. The rate of adverse events was higher in younger children (0–5 years) than in older children (6–11 years). As expected, this difference was mainly driven by frequent adverse events concerning common diseases in small children (e.g., nasopharyngitis and cough) and did not raise any safety concern.

PUPs: Of total 81 patients, 78 (96.3%) patients experienced 760 adverse events, corresponding to an adverse event rate of 3.39 events per PYE during the trial, which is comparable to the rate observed in children 0-5 yoa.

Severe AEs

PTPs: Nine AE in the 0-5 cohort and 4 AE in the 6 – 11 cohort were reported as severe. Most of these severe events were infections, a hypersensitivity reaction or injuries.

PUPs: The 31 severe AEs in 23 patients (28.4%) corresponded to a rate of 0.14 severe AEs per patient year and pertained in the majority to the development of inhibitors.

Related AEs

PTPs: A total of 21 adverse events in 14 children were evaluated by the investigator as possibly or probably related to N8-GP, corresponding to a rate of 0.07 and 0.04 events per PYE in younger children (0-5 years) and older children (6-11 years) respectively. All the adverse events (by PT) evaluated as possibly or probably related to N8-GP by the investigator in children were reported in single patients (2.9%); except for one related event of seizure which was reported in 2 (5.9%) patients.

PUPs: 27 events in 26 patients were judged as probably or possibly related to N8-GP by the investigator, most of which pertainted to the development of FVIII inhibitors.

Most Frequently Reported AEs

PTPs: In line with the safety profile observed in all treated patients irrespective of age, the most frequently reported AEs were in the SOC of injury, poisoning and precedural complications as well as infections and infestations.

PUPs: The most frequently reported AEs are in line with events expected in a young paediatric population, namely infections, pyrexia and accidents.

SAEs

PTPs: A review of all SAEs reported in the age group <12 yoa irrespective of causality did not reveal safety concerns. Most SAEs pertained to infections or injuries. The three SAEs assessed as possibly related by the investigator in paediatric patients were reported in the paediatric trial 3885 and the long-term extension trial 4410. The relationship between a seizure experienced at ED 10 and turoctocog beta pegol is considered unlikely. The narratives of the seizures reported in LTE trial 4410 do not support a causal relationship between the SAE and the medicinal product.

PUPs: A review of all SAEs in the PUP trial, irrespective of causality, revealed that most SAEs were either FVIII inhibitors or infections (e.g. bronchiolitis, RSV infection, pneumonia etc.). One cerebral haemorrhage in a toddler was the result of a fall down stairs. Another toddler experienced a cerebral haemorrhage and seizure in the context of high titre inhibitor development. A spontaneous epidural bleed was reported in another toddler, which resolved within 20 days. It is agreed with the MAH that all events except FVIII inhibition are considered unlikely related to turoctocog beta pegol.

Deaths

In the paediatric population, no fatal events were reporten in PUPs or PTPS. In the adult population, one death from pancreatic cancer occurred in the pivotal adolescent/adult trial for Esperoct, which was already assessed during the initial marketing authorisation procedure. An additional death from melanoma was recorded in the long-term extension trial 4410. Trial 4410 was assessed during the renewal procedure EMEA/H/C/004883/R/0022. It is agreed with the MAH that both events are unlikely related to Esperoct.

AESI/ AE related to theoretical PEG safety concerns

The following events were considered to be medical events of special interest in the N8-GP clinical trials: • Medication errors • Inhibitor formation against FVIII • Allergic reaction including anaphylactic reactions • Thromboembolic events. The SMQ searches 'acute renal failure' and 'drug-related hepatic disorders' were chosen because the kidneys and the liver are known sites of PEG elimination. The NNMQ search 'CNS events' consisting of the SOCs Nervous system disorders and Psychiatric disorders was chosen based on nonclinical studies.

No AEs in conjunction with medications errors were reported. Rash, erythema, pruritus and hypersensitivity are reflected as ADRs in section 4.8 of the SmPC. Injection site reactions were mostly due to the method of administration and not the medicinal product per se. No thromboembolic events occurred in paediatric PTPs, and the AEs in PUPs were all related to device or procedure malfunctions. Most hepatic AEs were connected to preexisting infections with hepatitis B or C. Very few renal AEs were reported in the clinical investigation programme and no safety issue arises from the renal AE profile. Most CNS related AEs reported in the paediatric study population concerned headache. The reported events of seizure appear to be related to other causative events, e.g. an intracerebral bleed as an infant, concomitant medication with methylphenidate (Ritalin), post-traumatic, fever and the development of an

inhibitor with a consecutive intracerebral bleed. Most subjects continued with their N8-GP treatment regimen. Further, the MAH submitted a justification for bridging of PEG-related clinical safety data available for N9-GP (Refixia) to N8-GP (Esperoct). N9-GP, a PEGylated recombinant factor IX (rFIX) product was approved in 2017 for use in patients aged 12 years and above. Recently an extension of indication (EMEA/H/C/004178/II/0032) to include all age groups was approved in August 2023. N9-GP demonstrated favourable prophylactic and haemostatic efficacy and safety in clinical trials across all age groups, and furthermore, provided extensive clinical PEG safety data showing no safety concerns related to long-term exposure to PEG. A comparison of the PEG moiety and steady-state PEG levels for the Esperoct and Refixia development programme support the extrapolation of the long-term clinical safety provided with Refixia to Esperoct, which is accepted.

Immunogenicity

The incidence of inhibitors observed in PUPs is in the range expected for patients with haemophilia and developed mostly before 20 exposure days, when the risk is highest.

Other ADAs investigated in the PTP trials (i.e. anti-N8-GP antibodies, anti-PEG antibodies and anti-CHO antibodies) do not appear to influence the safety or efficacy of Esperoct. It is however noted, that PTPs in the paediatric study 3885 who were positive for anti-PEG antibodies reached FVIII activity levels in the lower range of the observed values for the whole group.

In the PUP trial, anti-CHO antibodies occurred in a minority of subjects at low titres and were not associated with adverse events. Anti-N8-GP antibodies and anti-PEG-antibodies, however, reached relatively high titres and were slow to return to lower levels. While the titre of anti-N8-GP antibodies and anti-PEG IgM antibodies did not correlate with low measured IR values, the titre of anti-PEG IgG antibodies showed a high correlation and their presence was determined to be the root cause for low IR levels unexplained by an inhibitor in 17 patients. The phase with low IR was self-limited for the affected subjects, as the MAH states, but the duration of the low IR values of up to 60 exposure days gave rise to concern. The phase of low IR was associated with more severe bleeding events than reported for subjects with normal IR levels. 5 of the subjects experiencing repeated low IR withdrew, one for lack of efficacy, three due to adverse events and one due to decision of the PI. The MAH has clarified that the majority of the observed severe bleeds were of traumatic nature. Further, the incidence of spontaneous severe bleeds was comparable to that in PUPs with normal IR and the haemostatic response for treatment of bleeding events was similar in PUPs with and without low IR. Consequently, a warning statement was added to section 4.4 of the SmPC alerting the treating physician to the possibility of non-inhibitor related low IR in PUPs.

Post-marketing data

Post-marketing reports of the use of turoctocog alfa pegol in clinical practice in PTPS ≥12 years of age do not raise additional safety concerns.

2.5.2. Conclusions on clinical safety

The MAH has submitted a comprehensive dossier investigating the safety of long-term treatment with turoctocog alfa pegol in paediatric PTPs and PUPs. Exposures of more than 7 years were achieved during the extension phases of the trials 3885 in 68 PTPs. In PUP trial 3908, a total of 81 PUPs were exposed to N8-GP for a total of 18,184 EDs corresponding to a total of 233.8 PYE.

The observed adverse event profile was consistent with that observed in the already licensed population of adolescents and adults 12 years of age and older, with a higher incidence of infections and injuries as

usually observed in a young paediatric population. The incidence of inhibitors in PUPs was within the expected range.

The investigation of AESI and AEs related to the theoretical safety concerns of PEG exposure revealed no safety signal. In addition, the MAH submitted a justification for the bridging to the comprehensive safety data available for N9-GP (Refixia), which is a coagulation factor IX glykopegylated with an identical 40 kD PEG moiety.

The immunogenicity profile in PTPs was considered acceptable, but in PUPs the development of anti-PEG antibodies was associated with prolonged phases of low IR unexplained by the presence of an inhibitor in a substantial proportion of subjects (28.8%). This phase, albeit self-limited, persisted for up to 60 ED and led to an increase of severe bleeding events. This concern has been satisfactorily addressed and adequately reflected in section 4.4 of the SmPC.

In conclusion, the safety profile in previously treated paediatric subjects < 12 years of age did not differ in a relevant manner from that observed in older subjects treated with turoctocog alfa pegol. The number of exposed paediatric subjects surpasses guideline requirements. The duration of exposure is sufficient to allow the assessment of the long-term safety profile. The extension of indication to PTPs below 12 years of age is therefore approvable from a safety perspective.

The extension of indication to PUPs is also considered approvable, as the observed low IR in conjunction with anti-PEG antibodies is adequately reflected in the SmPC and as detailed bleeding and haemostatic response rate data alleviated previous concerns.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.1 is acceptable.

Safety concerns

Table 66: Summary of the Safety Concerns

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.

Pharmacovigilance plan

Table 67: 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 report	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

Risk minimisation measures

Table 68: Summary of pharmacovigilance and risk minimisation activities, by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		

Safety concern	Risk minimisation measures	Pharmacovigilance activities
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)
Allergic/hypersensitivity reactionss	*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	*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:*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None	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*:* *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	*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
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	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*: None *Additional pharmacovigilance activities:* None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None	
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.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, of the SmPC have been updated. Particularly, a new warning with regards to decreased factor VIII incremental recovery in previously untreated patients has been added to the product information. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed by QRD and accepted by the CHMP.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

User consultation was made for the marketing authorisation application approved in June 2019. The changes introduced within this variation are evaluated to be minor and are not significant.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Haemophilia A is a rare and serious, X-linked, recessive bleeding disorder that predominantly affects males and is characterised by a deficiency of FVIII. In patients with haemophilia A, the primary platelet-driven haemostasis is not affected, but generation of a stable, fibrin-rich clot is defective because inadequate amounts of thrombin are generated. Affected patients suffer from both spontaneous, non-traumatic bleeding episodes as well as substantially prolonged bleeding episodes upon injury. Rarely, life-threatening bleeding may also occur. Patients exhibit variable clinical phenotypes depending on the extent of residual activity (%) of the deficient FVIII that is used to classify the disease severity (WFH, 2012):

- <1% FVIII activity: severe haemophilia A
- 1% to 5% FVIII activity: moderate haemophilia A
- 5% to 40% FVIII activity: mild haemophilia A

Patients with severe haemophilia A bleed spontaneously into joints and muscles, which often results in permanent, disabling joint damage.

With this application, the MAH has applied to a paediatric extension of indication in patients < 12 years of age.

3.1.2. Available therapies and unmet medical need

Standard treatment for haemophilia A patients is the replacement of the missing protein by infusion of exogenous FVIII concentrates (as plasma-derived FVIII [pdFVIII] or recombinant FVIII [rFVIII] concentrates). Treatment regimens are either on-demand therapy (given when a bleed occurs) or prophylaxis (which consists of regular infusion of FVIII given every 2 to 3 days to prevent bleeding). In the short term, prophylaxis can prevent spontaneous bleeding and in the long term, prophylaxis can prevent bleeding into joints that will eventually lead to debilitating arthropathy.

Prior to the introduction of clotting factor concentrates in the 1960s, the prognosis for haemophilia A patients was poor, average life expectancy being 15 to 25 years. Major advances in the safety of clotting factor products, including the availability of rFVIII concentrates, the availability of comprehensive haemophilia A treatment centres, the institution of routine prophylaxis, the introduction of home treatment, as well as the active roles that patients take in self-advocacy, have enabled patients with haemophilia A to lead a "close to normal" life.

The recent development of FVIII products with extended half-lives has made it possible to maintain higher FVIII activity levels with fewer injections. Two other extended half-life FVIII products are currently licensed (Elocta and Adynovi). Hemlibra (emicizumab) has been recently authorised for routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors and without factor VIII inhibitors. In addition, a gene therapy Roctavian is indicated for the treatment of severe haemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5).

3.1.3. Main clinical studies

The main evidence supporting the extension of indication in children (<12 years of age) with haemophilia A is based on the data from PTP trial 3885 and PUP trial 3908. Additional information on long-term efficacy in PTPs derives from study 4410. 72 paediatric PTPs (<12 years old) were enrolled in trial 3885 (n=68 exposed to N8-GP) and 82 paediatric PUPs (0-5 years old) were enrolled in trial 3908 (n=81 exposed to N8-GP). PTPs were recommended to received routine prophylaxis treatment of N8-GP 60 IU/kg twice weekly, and PUPs could either enrol directly into prophylaxis at the same dose as PTPs or they could enter a pre-prophylaxis phase where they received N8-GP on demand. Safety data were enriched with data acquired from Refixia, a pegylated Factor IX product, in haemophilia B patients, in order to substantiate the claim that the pegylation does not constitute a major safety concern.

3.2. Favourable effects

No paediatric PTP developed confirmed FVIII inhibitors during trials 3885 and 4410.

A mean t1/2 of 13.9h and 14.6h is concluded for PTPs 0-5 years (n=15) and 6-11 years (n=12), respectively, after exposure to 50 IU/kg.

Mean Factor VIII trough levels in PTPs and PUPs were >1% throughout the observation period of up to 6 years.

Post-dose FVIII activity appears relatively stable for PTPs. The mean incremental recovery 30 minutes post-dose was >0.02 (IU/dL)/(IU/kg) throughout all visits for PTPs 6-11 years and no measurement was below 0.006 (IU/dL)/(IU/kg) in this age group.

The rate of breakthrough bleeds during prophylactic treatment in PTPs and PUPs suggests a successful control over the occurrence of bleeding events, at least with the applied dose level. Long-term efficacy in PTPs is further confirmed by results from study 4410.

Bleeding events in paediatric patients were mostly successfully treated with ≤2 injections of on-demand N8-GP.

3.3. Uncertainties and limitations about favourable effects

A high proportion of Factor VIII trough levels were below LLOQ.

Mean IR values in PTPs 0-5 years old were ≥ 0.017 (IU/dL)/(IU/kg), but a few measures were ≤0.006 (IU/dL)/(IU/kg).

The post-dose FVIII activity in PUPs was significantly reduced especially during early visits, resulting in a low IR (i.e. <0.6 (IU/dL)/(IU/kg)) for a large proportion of PUPs – of the 59 patients that did not develop inhibitors during study 3908, 17 patients were observed with consecutive low IRs and further 14 patients had a single measure of low IR. Consecutively low IR was associated with a reduced efficacy during the period of low IR in affected patients.

The rate of treatment failure in 6-11 year old PTPs appears relatively high (21.3% compared to 10.4% in 0-5 year old subjects), but was mostly related to moderate responses (19.8%).

3.4. Unfavourable effects

26% (21 of 81) of PUPs included in trial 3908 have developed Factor VIII inhibitors and 8 of these patients have initiated ITI treatment.

AE incidence

PTPs: In the adolescent patients (12–17 years), the rate of adverse events per PYE was slightly higher than in children (0-5 years and 6-11 years) and adults (≥18 years): 3.07 versus 2.96 (0–5 years), 2.38 (6-11 years) and 2.04 (≥18 years). However, the overall adverse event pattern in adolescents did not raise any safety concern; specifically, this age group did not have higher rates of serious adverse events, severe adverse events or events judged as possibly or probably related to N8-GP administration compared to the other age groups. The rate of adverse events was higher in younger children (0–5 years) than in older children (6–11 years). As expected, this difference was mainly driven by frequent adverse events concerning common diseases in small children (e.g., nasopharyngitis and cough) and did not raise any safety concern.

PUPs: Of a total of 81 patients, 78 (96.3%) patients experienced 760 adverse events, corresponding to an adverse event rate of 3.39 events per PYE during the trial, which is comparable to the rate observed in children 0-5 years of age.

Severe AEs

PTPs: Nine AE in the 0-5 cohort and 4 AE in the 6 – 11 cohort were reported as severe. Most of these severe events were infections, a hypersensitivity reaction or injuries.

PUPs: The 31 severe AEs in 23 patients (28.4%) corresponded to a rate of 0.14 severe AEs per patient year and pertained in the majority to the development of inhibitors.

Related AEs

PTPs: A total of 21 adverse events in 14 children were evaluated by the investigator as possibly or probably related to N8-GP, corresponding to a rate of 0.07 and 0.04 events per PYE in younger children (0-5 years) and older children (6-11 years) respectively.

PUPs: 27 events in 26 patients were judged as probably or possibly related to N8-GP by the investigator, most of which pertainted to the development of FVIII inhibitors.

Most Frequently Reported AEs

PTPs: In line with the safety profile observed in all treated patients irrespective of age, the most frequently reported AEs were in the SOC of injury, poisoning and precedural complications as well as infections and infestations.

PUPs: The most frequently reported AEs are in line with events expected in a young paediatric population, namely infections, pyrexia and accidents.

SAEs

PTPs: A review of all SAEs reported in the age group <12 years of age irrespective of causality did not reveal safety concerns. Most SAEs pertained to infections or injuries.

PUPs: A review of all SAEs in the PUP trial, irrespective of causality, revealed that most SAEs were either FVIII inhibitors or infections (e.g. bronchiolitis, RSV infection, pneumonia etc.). It is agreed with the MAH that all events except FVIII inhibition are considered unlikely related to turoctocog beta pegol.

AESI

The investigation of AESI and AEs related to the theoretical safety concerns of PEG exposure revealed no safety signal. In addition, the MAH submitted a justification for the bridging to the comprehensive safety data available for N9-GP (Refixia), which is a coagulation factor IX glykopegylated with an identical 40 kD PEG moiety.

No deaths occurred in the paediatric population.

Immunogenicity

The immunogenicity profile in PTPs was acceptable, but in PUPs the development of anti-PEG antibodies was associated with prolonged phases of low IR unexplained by an inhibitor in a substantial proportion of subjects (28.8%). This phase, albeit self-limited, persisted for up to 60 ED and led to an increase of severe bleeding events. Therefore, a warning on decreased factor VIII incremental recovery in previously untreated patients has been introduced in section 4.4 of the SmPC.

Post-marketing reports of the use of nonacog beta pegol in clinical practice do not raise additional safety concerns.

3.5. Uncertainties and limitations about unfavourable effects

While the number of exposed paediatric subjects surpasses FVIII guideline requirements, it is still relatively small, but, given the rarity of the disease this can be accepted. The duration of exposure is relatively long for a FVIII clinical investigation programme, allowing the assessment of the long-term safety profile. Furthermore, supportive data illustrating the safety profile in adolescents and adults treated with turoctocog alfa pegol and subjects of all ages treated with nonacog beta pegol have been provided to address uncertainties pertaining to the long-term use of PEGylated coagulation factors.

While the narratives of the SAEs do not indicate a relationship to Esperoct, it is noticed that two seizures were reported where the aetiology is unclear. In addition, to address concerns in relation to PEG raised during initial MAA, the MAH referred to the data generated for Refixia and submitted these data in the current application of Esperoct.

3.6. Effects Table

Table 69: Effects Table for Esperoct, extension of indication to children <12 years of age

Effect	Short description	Treatment dose	Outcome			
			Unit	PTP 0-5 years	PTP 6-11 years	PUPs
Favourable Effects						
Incremental recovery	FVIII levels by dose administered per kg 60 minutes (PTP) or 30 minutes (PUP) post dose	60 IU/kg	IU/mL/ IU/kg	0.017 (0.014; 0.021)	0.22 (0.018; 0.027)	Mostly ~0.015 to ~0.025, BUT 17/59 (29%) without inhibitors developed consecutively low IR# AND 14/59 (24%) had single low IR# measures
Annualised bleeding rate	Breakthrough bleeding events during prophylaxis Mean ABR (poisson	60 IU/kg twice weekly	Events/year (95% CI)	1.04 (0.45; 2.40)	1.18 (0.84; 1.66)	1.76 (1.26; 2.46)

Effect	Short description	Treatment dose	Outcome			
			Unit	PTP 0-5 years	PTP 6-11 years	PUPs
	estimate)					
Haemostatic response	Treatment of all bleeds: Treatment success	60 IU/kg twice weekly	% (95% CI)	90.8 (80.2; 96.0)	84.3 (76.8; 89.8)	92.5 (88.5; 95.2)
Treatment of bleeding events	Bleeds treated with 1-2 injections	60 IU/kg	%	90.2	89.3	93.3
Unfavourable Effects						
AE incidence			events per PYE	2.96	2.38	3.39
Related AE incidence			events per PYE	0.07	0.04	0.25
Inhibitor incidence			%	0.0		30.0
Anti PEG IgG antibodies			% (n/N)	1.5 (1/68)		63 (51/81)

Abbreviations: PYE: Patient Years of Exposure

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The prophylactic treatment with Esperoct is supported by stable mean Factor VIII levels (pre- and post-dose) for a long treatment duration (i.e. above the range of severe haemophilia A for up to 6 years) and is further substantiated by low bleeding rates in paediatric PTPs. However, a large proportion of PUPs had low IR for up to 60EDs. Even though the prophylactic control over bleeding was principally acceptable in the general population of PUPs and for the total study duration (mean number of EDs per patient was 235.4 EDs), consecutively low IR appears associated with reduced efficacy during the period of low IR (i.e. a higher rate of patients with bleeds, a higher rate of patients with spontaneous bleeds, more severe bleeding events and lower success rate for the haemostatic response compared to patients without consecutively low IR). These findings are reflected in section 4.4 of the SmPC. The haemostatic response for treatment of breakthrough bleeds was acceptable for paediatric PTPs and PUPs. Of note, the actual consumption of N8-GP during paediatric studies indicate that higher dose levels are required than the used 60 IU/kg during paediatric studies. The recommended dose for paediatric patients in the PI is acknowledged (i.e. 65 IU/kg (50-75 IU/kg)). In conclusion, efficacy data generally support the treatment of paediatric patients with N8-GP.

The safety profile in children regarding the overall adverse event pattern was in principle consistent with that observed in the already licensed population of adolescents and adults ≥12 years of age. The long duration of observation is reassuring regarding the long-term safety profile. The number of paediatric patients fulfils GL requirements and can be accepted, given the rarity of the disease. The higher rate of adverse events in younger children (0–5 years) compared to older children (6–11 years) was expected, as it is related to frequent adverse events in small children, e.g. infections. No new or unusual AEs were observed and reported SAEs did not reveal safety concerns in paediatric patients. The incidence of inhibitors in PUPs was within the expected range. It is reassuring that the safety profile in PUPs was

mostly comparable to PTPs 0-5 years old. The development of anti-PEG antibodies in PUPs was associated with prolonged phases of low IR unexplained by an inhibitor in a substantial proportion of patients, which is addressed with a warning statement in section 4.4 in the SmPC. The main safety concern raised during initial MAA and preventing a positive B/R balance in children below 12 years of age pertained to theoretical concerns with regards to PEG moiety of the product. The MAH did address this concern by referring to comprehensive data generated for Refixia (nonacog beta pegaol), a FIX product glycopegylated with an identical PEG molecule. Bridging of these data to Esperoct is accepted, and the relevant study reports were submitted as part of the dossier for Esperoct.

3.7.2. Balance of benefits and risks

Beneficial effects of N8-GP in paediatric patients were demonstrated both for the prophylactic setting as well as for the on-demand treatment of bleeding episodes. The long-term safety profile in children <12 years of age was benign with no new safety signals compared to the safety profile in adolescents and adults. The rate of inhibitor development in PUPs was consistent with such rates reported in the literature. The theoretical safety concerns in relation to the PEG moiety of the molecule can be considered resolved by bridging to extensive data generated for Refixia (nonacog beta pegol, which is glycopegylated with an identical PEG moledule).

Of note, consecutively low IR was observed in a substantial proportion of PUPs. The period of low IR persisted up to 60 EDs and was associated with anti-PEG IgG antibodies and reduced efficacy during the period of low IR, leading to a warning statement in section 4.4 of the SmPC.

The benefit/risk ratio in PTPs and PUPs is positive.

3.7.3. Additional considerations on the benefit-risk balance

Not Applicable.

3.8. Conclusions

The overall B/R of Esperoct is positive in the extension of indication to include children below 12 years of age for treatment and prophylaxis of bleeding with haemophilia A for Esperoct.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include children below 12 years of age for treatment and prophylaxis of bleeding with haemophilia A for Esperoct, including previously untreated patients (PUPs) based on the

final results from studies 3776, 4410, 3908, 3859, 3885, 3860, 4033 and 4595. As a consequence, section 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.1 of the RMP has also been submitted. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0142/2017 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Esperoct is not similar to Roctavian within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Esperoct H-C-004883/II/0023

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 04 October 2024. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by 04 October 2024. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. If a revised RMP is being approved as part of this procedure, **please send to the EMA Procedure Assistant** one redacted PDF document containing the RMP body, Annex 4 and Annex 6, as applicable, together with a redacted RMP file that can show the content that is proposed for redaction, and the signed RMP Publication Declaration, **by** 04 October 2024.