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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Refixia

Nonacog beta pegol

Procedure no: EMEA/H/C/004178/P46/008

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	24.06.2024	24.06.2024
☐	CHMP Rapporteur Assessment Report	29.07.2024	29.07.2024
☐	CHMP members comments	12.08.2024	12.08.2024
☐	Updated CHMP Rapporteur Assessment Report	16.08.2024	16.08.2024
☐	Request for Supplementary Information	22.08.2024	22.08.2024
☐	Submission	12.09.2024	12.09.2024
☐	Re-start	18.09.2024	18.09.2024
☐	CHMP Rapporteur Assessment Report	02.10.2024	30.09.2024
☐	CHMP members comments	07.10.2024	N/A
☐	Updated CHMP Rapporteur Assessment Report	10.10.2024	N/A
☒	CHMP adoption of conclusions:	17.10.2024	17.10.2024

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1. Introduction

On 16 May 2024, the MAH submitted a completed paediatric study for Refixia, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study NN7999-3774 is part of a clinical development program. The variation application consisting of the full relevant data package (i.e containing several studies) was submitted in November 2022. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

Refixia powder and solvent for solution for injection. The powder is white to off-white. The solvent is clear and colourless. pH: 6.4. Osmolality: 272 mOsmol/kg.

Refixia is a purified recombinant human factor IX (rFIX) with a 40 kDa polyethylene-glycol (PEG) selectively attached to specific N-linked glycans in the rFIX activation peptide. Upon activation of Refixia, the activation peptide including the 40 kDa polyethylene-glycol moiety is cleaved off, leaving the native activated factor IX molecule. The primary amino acid sequence of the rFIX in Refixia is identical to the Ala148 allelic form of human plasma-derived factor IX. No additives of human or animal origin are used in the cell culture, purification, conjugation, or formulation of Refixia.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

- Study NN7999-3774: An open-label, single-arm, multinational, non-controlled, confirmatory trial investigating safety, efficacy and pharmacokinetics of nonacog beta pegol (N9-GP) in prophylaxis and treatment of breakthrough bleeding episodes in previously treated children with haemophilia B (12 years of age and younger at inclusion)".

2.3.2. Clinical study

Safety, Efficacy and Pharmacokinetics of NNC-0156-0000-0009 (nonacog beta pegol, N9-GP) in Previously Treated Children with Haemophilia B

Description

An open-label, single-arm, multinational, non-controlled, confirmatory trial investigating safety, efficacy and pharmacokinetics of NNC-0156-0000-0009 (nonacog beta pegol, N9-GP) in prophylaxis and treatment of breakthrough bleeding episodes in previously treated children with haemophilia B (12 years of age and younger at inclusion).

Methods

Study participants

Inclusion criteria

For an eligible patient, all inclusion criteria must be answered "yes". According to the protocol, the inclusion criteria were as follows.

1. Informed consent obtained before any trial-related activities. (Trial-related activities are any procedure that would not have been performed during normal management of the patient)

2. Male patients with moderately severe or severe congenital haemophilia B with a FIX activity level ≤2% according to medical records.

3. Age ≤12 years (until patient turns 13 years, at time of inclusion).

4. Body weight ≥10 kg.

5. History of at least 50 exposure days (EDs) to other FIX products.

6. The patient and/or parent(s)/caregiver are capable of assessing a bleeds, 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 must be answered "no". Key exclusion criteria are presented below. The complete list of exclusion criteria is provided in the trial protocol.

1. Known history of FIX inhibitors.

2. Current FIX inhibitors ≥0.6 Bethesda Units (BU).

3. Congenital or acquired coagulation disorder other than haemophilia B.

4. Platelet count <50,000/µL at screening.

5. Alanine aminotransferase (ALT) >3 times the upper limit of normal reference ranges at screening.

6. Creatinine level ≥1.5 times above the upper normal limit of normal reference ranges at screening.

7. Human immunodeficiency virus (HIV) positive, defined by medical records, and with a CD4+ lymphocyte count ≤200/µL.

8. Immune modulating or chemotherapeutic medication (except single pulse treatment, inhaled and topical steroids).

9. Previous arterial thrombotic events (myocardial infarction and intracranial thrombosis, as defined by medical records).

Treatments

Prophylaxis: 40 IU/kg once weekly

Surgery: 40 IU/kg for minor surgery; 80 IU/kg for major surgery

Treatment of bleeds: 40 IU/kg (mild/moderate); 80 IU/kg (severe)

Objective(s)

Trial 3774 (PTPs) consisted of a main phase (≥52 weeks) and an extension phase of up to 10 years. The results from the main phase were submitted with the original file in 2016, while the interim report covering the main phase and extension data up to the interim cut-off date (25-Nov-2020) are provided in this type II variation application for extension of indication to include paediatric population.

Trial 3774 was initiated on 16-May-2012. It comprises a ≥52-week main phase and an up to 10-year extension phase (consisting of patients who completed the main phase) in younger (0-6 years) and older (7-12 years) PTPs. Patients in both phases received a single 40 IU/kg once weekly dose of nonacog beta pegol for prophylaxis. Given the long duration of the trial, paediatric patients became adolescents or adults at some point during the trial.

Primary objective

• To evaluate immunogenicity of N9-GP

Secondary objectives

• To evaluate safety other than immunogenicity of N9-GP

• To evaluate the efficacy of N9-GP in long-term prophylaxis and in the treatment of breakthrough bleeding episodes

• To evaluate the efficacy of N9-GP through the surrogate marker for efficacy, FIX activity

• To evaluate the PK properties of N9-GP

• To evaluate patient reported outcomes (PROs) and assess health economic impact of treatment with N9-GP

Outcomes/endpoints

Primary endpoint

- Incidence of inhibitory antibodies against FIX defined as titre ≥0.6 BU

Secondary endpoints

Safety endpoints:

- Adverse events including serious adverse events (SAEs) and medical events of special interest (MESI), and development of host cell protein (HCP) antibodies

Efficacy endpoints:

- Number of bleeding episodes during prophylaxis
- Haemostatic effect of N9-GP in treatment of bleeding episodes by 4-point categorical scale for haemostatic response (excellent, good, moderate and poor)
- FIX consumption described as frequency of dose/kg for prophylaxis use and number of doses and amount consumed for the treatment of bleeding episodes

Pharmacokinetic endpoints:

- Pharmacokinetic endpoints, except trough steady state and FIX activity at 30 minutes (C30min) steady state, are assessed after a single dose (Visit 2). Steady state trough and C30min will be assessed at Visit 4 - Visit 10 during the main phase of the trial.

- Incremental recovery at 30 minutes (IR30min) ([U/mL] / [U/kg])
- Trough level (U/mL) (single-dose and steady state)
- Area under the curve (AUC) (Uxh/mL)
- Terminal half-life (t1/2) (h)
- Clearance (CL) (mL/h/kg)
- Mean residence time (MRT) (h)
- Volume of distribution at steady state (Vss) (mL/kg)
- FIX activity at 30 minutes (C30min) (U/mL) (single-dose and steady state)

Patient reported outcomes and health economic endpoints:

- Changes in health related quality of life (HRQOL) from Visit 1 to Visit 11 and to end of trial visit (EOT), assessed using age and disease specific patient reported outcomes (PRO) questionnaires: Haemophilia-quality of life (HAEMO-QOL), Hemophilia treatment satisfaction (HEMO-SAT), and TNO-AZL preschool quality of life (TAPQOL)
- Health economic impact of N9-GP treatment through characterisation of hospitalisations, emergency room visits, missed work and/or school days, and mobility aid requirements

Sample size

No formal sample size calculations have been performed. The sample size is based on the requirements in the EMA guideline. Around 40 patients will be screened in order to start approximately 24 patients on trial product out of which 10 patients in each of the two age groups are expected to complete the main phase of the trial. The patients will be stratified into two age groups; 0-6 years and 7-12 years, both inclusive. A minimum of 10 patients in each age group must complete the main phase of the trial. The trial has one treatment arm where all patients receive N9-GP once weekly for prophylaxis. In the extension phase, the investigator is allowed to individualise both dose levels and/or dosing frequency. Treatment with N9-GP will in addition be administered in case of breakthrough bleeding episodes.

Randomisation and blinding (masking)

No randomisation was performed due to the single-arm nature of the paediatric trial.

Blinding does not apply as the submitted paediatric trial was an open-label trial.

Statistical Methods

Except for the confidence interval for inhibitor rate and for annualised bleeding rate, the evaluation of data will be based on descriptive statistics, i.e. summary tables, listings and figures. Multiple bleeding locations occurring from the same event (e.g., due to a bicycle accident) or at the same time point will be counted as one bleeding episode. In general all summaries and analyses will also be made by age subgroup (0-6 and 7-12 years of age). The following analysis sets were defined in the protocol:

Full analysis set (FAS) included all patients with efficacy data after exposure to nonacog beta pegol. The analysis of efficacy and PK data was based on FAS.

Safety analysis set (SAS) included all patients exposed to nonacog beta pegol. The safety analysis was based on the safety analysis set.

FAS and SAS were identical in the main phase and extension phase of the trial.

Results

Participant flow

A total of 28 patients were screened for this trial, of which 3 were screen failures. A total of 25 (100.0%) patients were exposed to the trial product in the main phase, of which 12 (100.0%) patients were in the 0-6 year age group and 13 (100.0%) were in 7-12 year age group. One (1) patient from 0-6 year age group withdrew from the main phase. 24 (96.0%) patients completed the main phase of the trial. Of the 25 exposed patients, 22 (88.0%) patients entered the extension phase of the trial, of which 11 (91.7%) patients were in the 0-6 year age group and 11 (84.6%) patients were in the 7-12 year age group. During the extension phase 12 (48.0%) patients withdrew from the trial. All withdrawn patients contributed with data until the date of withdrawal.

Table 1: Patient disposition

	Younger children (0 - 6 years)	Older children (7 - 12 years)	Total
Screened	13	15	28
Exposed, N(%)	12 (100.0)	13 (100.0)	25 (100.0)
Completed main phase, N(%)	11 (91.7)	13 (100.0)	24 (96.0)
Withdrawal during main phase, N(%)	1 (8.3)	- (-)	1 (4.0)
Withdrawal of consent	1 (8.3)	- (-)	1 (4.0)
Not continuing in extension phase, N(%)	- (-)	2 (15.4)	2 (8.0)
Withdrawal criteria	- (-)	2 (15.4)	2 (8.0)
Entered extension phase, N(%)	11 (91.7)	11 (84.6)	22 (88.0)
Withdrawal during extension phase, N(%)	5 (41.7)	7 (53.8)	12 (48.0)
Non-compliance	- (-)	1 (7.7)	1 (4.0)
Withdrawal criteria	- (-)	2 (15.4)	2 (8.0)
Withdrawal of consent	2 (16.7)	1 (7.7)	3 (12.0)
Other	3 (25.0)	3 (23.1)	6 (24.0)
Full analysis set, N(%)	12 (100.0)	13 (100.0)	25 (100.0)
Safety analysis set, N(%)	12 (100.0)	13 (100.0)	25 (100.0)
Undergone minor surgery, N(%)	6 (50.0)	6 (46.2)	12 (48.0)
Undergone major surgery, N(%)	1 (8.3)	- (-)	1 (4.0)
Years in trial*	96.0	88.5	184.4
EDs in trial	5034	4631	9665

ED: Exposure days.
%: Patients exposed to N9-GP considered for denominator for percentage calculation.
* Years in trial: Sum of years in trial for all patients.
The full analysis set and the safety analysis set both consist of all patients exposed to nonacog beta pegol.

Recruitment

Table 2: Screening failures

Subject identifier for the study	Age at baseline	Country	Race	Ethnicity	Stop date	Exposed	Specification of other failure reason	Inclusion criteria as failure reason	Exclusion criteria as failure reason
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	No			E4
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	No			E5
[redacted]	[redacted]	[redacted]			[redacted]	No	Normal clinic procedure requires patients get v/s and weight before any visit; patient's BMI disqualified [redacted] from participation, thus no consent was signed and no study procedures were done.		E4

E4 = Documented diagnosis of obesity defined as body mass index (BMI) equal to or greater than the 95th percentile for age for children ≥2 years. E5 = Known history of FIX inhibitors based on existing medical records, laboratory report reviews and patient/caregiver interviews.

Baseline data

Table 3: Baseline demographics - full analysis set

	Younger children (0-6 years)	Older children (7-12 years)	Total
Number of patients	12	13	25
Age at baseline (years)			
N	12	13	25
Mean (SD)	3.1 (1.7)	9.6 (1.6)	6.5 (3.7)
Median	3.0	10.0	7.0
Min ; Max	1 ; 6	7 ; 12	1 ; 12
Country, N (%)			
N	12 (100.0)	13 (100.0)	25 (100.0)
Canada	1 (8.3)	3 (23.1)	4 (16.0)
Germany	1 (8.3)	-	1 (4.0)
Italy	1 (8.3)	-	1 (4.0)
Japan	1 (8.3)	2 (15.4)	3 (12.0)
Malaysia	-	2 (15.4)	2 (8.0)
Taiwan	2 (16.7)	-	2 (8.0)
United Kingdom	3 (25.0)	-	3 (12.0)
United States of America	3 (25.0)	6 (46.2)	9 (36.0)
Ethnicity, N (%)			
N	12 (100.0)	13 (100.0)	25 (100.0)
Hispanic or Latino	-	2 (15.4)	2 (8.0)
Not Hispanic or Latino	12 (100.0)	11 (84.6)	23 (92.0)
Race, N (%)			
N	12 (100.0)	13 (100.0)	25 (100.0)
Asian	4 (33.3)	4 (30.8)	8 (32.0)
Black or African American	-	1 (7.7)	1 (4.0)
White	8 (66.7)	5 (38.5)	13 (52.0)
Other	-	3 (23.1)	3 (12.0)

SD: Standard Deviation

Table 4: Haemophilia and inhibitor history - full analysis set

	Younger children (0-6 years)	Older children (7-12 years)	Total
Number of patients	12	13	25
Classification of haemophilia B*, N (%)			
N	12 (100.0)	13 (100.0)	25 (100.0)
Severe	12 (100.0)	13 (100.0)	25 (100.0)
Have FIX level (%) from medical history**, N (%)			
N	12 (100.0)	13 (100.0)	25 (100.0)
Yes	12 (100.0)	13 (100.0)	25 (100.0)
FIX level (%) from medical history**			
N	2	1	3
Mean (SD)	1.1 (0.1)	1.0 (-)	1.1 (0.1)
Median	1.1	1.0	1.0
Min ; Max	1.0 ; 1.2	1.0 ; 1.0	1.0 ; 1.2
FIX level (%) from medical history in ranges**, N (%)			
N	10 (100.0)	12 (100.0)	22 (100.0)
<0.6%	2 (20.0)	-	2 (9.1)
<1.0%	8 (80.0)	12 (100.0)	20 (90.9)
FIX level (%) at screening***			
N	11	13	24
Mean (SD)	2.1 (0.7)	4.6 (1.7)	3.4 (1.8)
Median	2.2	4.9	2.7
Min ; Max	0.8 ; 3.5	2.5 ; 8.0	0.8 ; 8.0
History of haemophilia B among relatives, N (%)			
N	12 (100.0)	13 (100.0)	25 (100.0)
Yes	3 (25.0)	3 (23.1)	6 (24.0)
No	7 (58.3)	9 (69.2)	16 (64.0)
Unknown	2 (16.7)	1 (7.7)	3 (12.0)
Relatives with haemophilia B†, N (%)			
N	3 (100.0)	3 (100.0)	6 (100.0)
None	1 (33.3)	1 (33.3)	2 (33.3)
Maternal grandfather, siblings / cousins	-	2 (66.7)	2 (33.3)
Maternal uncle	1 (33.3)	-	1 (16.7)
Missing†	1 (33.3)	-	1 (16.7)
Clinical suspicion of inhibitors, N (%)			
N	12 (100.0)	13 (100.0)	25 (100.0)
No	12 (100.0)	13 (100.0)	25 (100.0)
Number of FIX peak tests within 5 years††			
N	11	13	24
Mean (SD)	2.6 (2.4)	1.5 (1.6)	2.0 (2.1)
Median	2.0	1.0	2.0
Min ; Max	0.0 ; 7.0	0.0 ; 6.0	0.0 ; 7.0
Number of inhibitor tests within 5 years			
N	12	13	25
Mean (SD)	4.0 (3.3)	3.7 (2.7)	3.8 (3.0)
Median	4.0	4.0	4.0
Min ; Max	0.0 ; 12.0	0.0 ; 10.0	0.0 ; 12.0
Other coagulation related diseases†††, N (%)			
N	12 (100.0)	13 (100.0)	25 (100.0)
No	3 (25.0)	2 (15.4)	5 (20.0)
Missing	9 (75.0)	11 (84.6)	20 (80.0)

* If classified as mild, inclusion criteria 2 is violated.
** Patients could either report the value as numeric or in ranges.
*** One patient had insufficient specimen volume.
† N refers to the patients with answer 'Yes' to the question. One patient has answered 'Yes' and not replied on the following question about relatives.
†† One patient did not report FIX peak test result.
††† If yes, should be excluded according to exclusion criteria 7.

Number analysed

All 25 exposed patients contributed to the Full analysis set and Safety analysis set.

Table 5: Nonacog beta pegol exposure - full analysis set

	Younger children (0-6 years)	Older children (7-12 years)	Total
Number of patients	12	13	25
Total number of doses per patient			
N	12	13	25
Mean (SD)	419.8 (190.6)	356.8 (205.7)	387.0 (197.1)
Median	482.5	359.0	413.0
Min ; Max	10.0 ; 580	53.0 ; 597	10.0 ; 597
Total number of exposure days per patient			
N	12	13	25
Mean (SD)	419.5 (190.6)	356.2 (205.7)	386.6 (197.1)
Median	482.5	358.0	413.0
Min ; Max	10.0 ; 580	53.0 ; 597	10.0 ; 597
Total number of prophylaxis doses per patient			
N	12	13	25
Mean (SD)	412.7 (188.2)	346.5 (204.5)	378.2 (195.7)
Median	475.0	352.0	408.0
Min ; Max	10.0 ; 580	51.0 ; 591	10.0 ; 591
Total number of doses used for treatment of bleed per patient			
N	9	12	21
Mean (SD)	8.3 (8.6)	10.8 (10.2)	9.7 (9.4)
Median	4.0	6.0	6.0
Min ; Max	1.0 ; 25.0	2.0 ; 30.0	1.0 ; 30.0
Total number of doses used for minor surgery per patient			
N	5	5	10
Mean (SD)	1.8 (1.3)	1.0 (0.0)	1.4 (1.0)
Median	1.0	1.0	1.0
Min ; Max	1.0 ; 4.0	1.0 ; 1.0	1.0 ; 4.0
Total number of doses used for major surgery per patient			
N	1	0	1
Mean (SD)	2.0 (-)	- (-)	2.0 (-)
Median	2.0	-	2.0
Min ; Max	2.0 ; 2.0	- ; -	2.0 ; 2.0
Treatment period per patient (years)			
N	12	13	25
Mean (SD)	8.0 (3.6)	6.8 (4.0)	7.4 (3.8)
Median	9.2	7.7	8.1
Min ; Max	0.2 ; 11.1	1.0 ; 11.4	0.2 ; 11.4

Efficacy results

Annualised bleeding rate (ABR)

Table 6: Annualised bleeding rate - full analysis set

	Younger children (0 - 6 years)	Older children (7 - 12 years)	Total
Number of patients	12	13	25
Number of patients with bleeds, N(%)	9 (75.0)	12 (92.3)	21 (84.0)
Number of patients with 0 bleeds, N(%)	3 (25.0)	1 (7.7)	4 (16.0)
Number of bleeds	63	86	149
Bleeds per patient (min ; max)	0 ; 22	0 ; 19	0 ; 22
Mean treatment period (years)	8.00	6.81	7.38
Individual ABRs			
N	12	13	25
Mean (SD)	0.62 (0.77)	1.45 (1.73)	1.05 (1.39)
Median	0.33	0.78	0.47
Interquartile range	0.05 ; 0.87	0.35 ; 1.73	0.28 ; 1.68
Min ; Max	0.00 ; 2.18	0.00 ; 6.38	0.00 ; 6.38
Poisson estimate of ABR	0.66	0.97	0.81
95% CI	0.34 ; 1.28	0.50 ; 1.91	0.50 ; 1.31
Negative binomial estimate of ABR	0.66	1.32	1.00
95% CI	0.32 ; 1.36	0.72 ; 2.41	0.62 ; 1.62
LOCF sensitivity analysis			
Number of patients with less than 30 days of exposure	0	0	0
Number of patients with LOCF*	6	7	13
Bleeds per patient (min ; max)	0 ; 24	0 ; 70	0 ; 70
Mean treatment period (years)	9.95	9.54	9.73
Poisson estimate of ABR	0.53	0.69	0.61
95% CI	0.26 ; 1.07	0.41 ; 1.18	0.40 ; 0.94
Negative binomial estimate of ABR	0.51	0.81	0.67
95% CI	0.25 ; 1.06	0.46 ; 1.41	0.42 ; 1.05

ABR: annualised bleeding rate, SD: standard deviation, CI: confidence interval,
LOCF: last observation carried forward.
* Number of withdrawals with at least 1 month of treatment.
Based on a Poisson regression model with age group as a factor allowing for over-dispersion and using treatment duration as an offset
A sensitivity analysis was carried out using the negative binomial model with treatment duration as an offset.
A confidence interval is only presented if there are at least 5 patients in the subgroup.

Annualised bleeding rate by type of bleeding episodes

At end of study, the observed mean (SD) ABR of spontaneous bleeding episodes was:

- 0.12 (0.24) bleeds/patient/year for patients in the younger children (0-6 years) group
- 0.32 (0.50) bleeds/patient/year for patients in the older children (7-12 years) group

The estimated ABR of spontaneous bleeding episodes based on the Poisson regression model was:

- 0.11 [0.04; 0.32]95%CI bleeds/patient/year for patients in the younger children (0-6 years) group
- 0.38 [0.17; 0.85]95%CI bleeds/patient/year for patients in the older children (7-12 years) group

At end of study, the observed mean (SD) ABR of traumatic bleeding episodes was:

- 0.49 (0.59) bleeds/patient/year for patients in the younger children (0-6 years) group
- 0.81 (1.47) bleeds/patient/year for patients in the older children (7-12 years) group

The estimated ABR of traumatic bleeding episodes based on the Poisson regression model was:

- 0.53 [0.27; 1.04]95%CI bleeds/patient/year for patients in the younger children (0-6 years) group

- 0.54 [0.21; 1.42]95%CI bleeds/patient/year for patients in the older children (7-12 years) group

Table 7: Annualised bleeding rates by actual age groups - full analysis set

	Younger children (0 - 6 years)	Older children (7 - 12 years)	Adolescents (13 - 17 years)	Adults (18 - 70 years)	Total
Number of patients	12	23	14	6	25
Number of patients with bleeds, N(%)	7 (58.3)	16 (69.6)	10 (71.4)	3 (50.0)	21 (84.0)
Number of patients with 0 bleeds, N(%)	5 (41.7)	7 (30.4)	4 (28.6)	3 (50.0)	4 (16.0)
Number of bleeds	35	75	32	7	149
Bleeds per patient (min ; max)	0 ; 11	0 ; 17	0 ; 12	0 ; 4	0 ; 22
Mean treatment period (years)	2.85	3.54	3.82	2.55	7.38
Individual ABRs					
N	12	23	14	6	25
Mean (SD)	0.67 (0.73)	1.59 (2.33)	0.51 (0.67)	0.30 (0.43)	1.05 (1.39)
Median	0.55	0.52	0.27	0.15	0.47
Interquartile range	0.00 ; 1.31	0.00 ; 2.22	0.00 ; 0.62	0.00 ; 0.41	0.28 ; 1.68
Min ; Max	0.00 ; 1.92	0.00 ; 9.25	0.00 ; 2.40	0.00 ; 1.11	0.00 ; 6.38
Poisson estimate of ABR	1.02	0.92	0.60	0.46	0.81
95% CI	0.68 ; 1.54	0.47 ; 1.78	0.32 ; 1.12	0.22 ; 0.97	0.50 ; 1.31

Age groups are based on actual age, therefore some patients are represented in multiple columns.
ABR: annualised bleeding rate, SD: standard deviation, CI: confidence interval.
Based on a poisson regression model with age group as a factor allowing for over-dispersion and using treatment duration as an offset.
A confidence interval is only presented if there are at least 5 patients in the subgroup.

Target Joints

Table 8: Target joints - full analysis set

	Younger children 0 - 6 years	Older children 7 - 12 years	Total
Number of patients	12	13	25
Number of patients with target joints at baseline*	0 (0.0)	2 (15.4)	2 (8.0)
Number of patients with no bleeds in target joints during trial**	0 (0.0)	0 (0.0)	0 (0.0)
Number of patients without target joints at baseline with 3 or more bleeds in a joint location within a 6 month period during trial ***	0 (0.0)	1 (9.1)	1 (4.3)
Number of bleeds involving a target Joint+	0 (0.0)	3 (3.5)	3 (2.0)
N	0 (0.0)	3 (100.0)	3 (100.0)
Spontaneous	0 (0.0)	0 (0.0)	0 (0.0)
Traumatic	0 (0.0)	3 (100.0)	3 (100.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)

*A target joint is defined as three or more bleeds in a period of 6 months in a particular joint.
**joints that were target joints at baseline, but where no bleeds occurred during the trial.
Percentage is out of number of patients with target joints at baseline.
***3 bleeds within a 6 month period. Percentage is out of number of patients without target joints at baseline.
+If one of the locations related to a bleed involves a baseline target joint, this count as a target bleed.

Haemostatic effect of nonacog beta pegol in treatment of bleeding episodes

Table 9: Haemostatic response - full analysis set

	Younger children (0 - 6 years)	Older children (7 - 12 years)	Total
Number of patients	12	13	25
Number of patients with bleeds, N(%)	9 (75.0)	12 (92.3)	21 (84.0)
Number of patients with 0 bleeds, N(%)	3 (25.0)	1 (7.7)	4 (16.0)
Number of bleeds	63	86	149
Haemostatic response, N(%)			
N	63 (100.0)	86 (100.0)	149 (100.0)
Excellent	29 (46.0)	25 (29.1)	54 (36.2)
Good	27 (42.9)	52 (60.5)	79 (53.0)
Moderate	4 (6.3)	7 (8.1)	11 (7.4)
Poor	2 (3.2)	2 (2.3)	4 (2.7)
Missing	1 (1.6)	0 (0.0)	1 (0.7)
Success/failure, N(%)			
N	62 (100.0)	86 (100.0)	148 (100.0)
Success	56 (90.3)	77 (89.5)	133 (89.9)
Failure	6 (9.7)	9 (10.5)	15 (10.1)
Success/failure (incl. missing as failure), N(%)			
N	63 (100.0)	86 (100.0)	149 (100.0)
Success	56 (88.9)	77 (89.5)	133 (89.3)
Failure	7 (11.1)	9 (10.5)	16 (10.7)

A successfully treated bleed is a bleeding episode where the treatment response was excellent or good.

Table 10: Haemostatic response by actual age groups - full analysis set

	Younger children (0 - 6 years)	Older children (7 - 12 years)	Adolescents (13 - 17 years)	Adults (18 - 70 years)	Total
Number of patients	12	23	14	6	25
Number of patients with bleeds, N(%)	7 (58.3)	16 (69.6)	10 (71.4)	3 (50.0)	21 (84.0)
Number of patients with 0 bleeds, N(%)	5 (41.7)	7 (30.4)	4 (28.6)	3 (50.0)	4 (16.0)
Number of bleeds	35	75	32	7	149
Haemostatic response, N(%)					
N	35 (100.0)	75 (100.0)	32 (100.0)	7 (100.0)	149 (100.0)
Excellent	18 (51.4)	27 (36.0)	6 (18.8)	3 (42.9)	54 (36.2)
Good	13 (37.1)	42 (56.0)	20 (62.5)	4 (57.1)	79 (53.0)
Moderate	2 (5.7)	5 (6.7)	4 (12.5)	0 (0.0)	11 (7.4)
Poor	2 (5.7)	0 (0.0)	2 (6.3)	0 (0.0)	4 (2.7)
Missing	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.7)
Success/failure, N(%)					
N	35 (100.0)	74 (100.0)	32 (100.0)	7 (100.0)	148 (100.0)
Success	31 (88.6)	69 (93.2)	26 (81.3)	7 (100.0)	133 (89.9)
Failure	4 (11.4)	5 (6.8)	6 (18.8)	0 (0.0)	15 (10.1)
Success/failure (incl. missing as failure), N(%)					
N	35 (100.0)	75 (100.0)	32 (100.0)	7 (100.0)	149 (100.0)
Success	31 (88.6)	69 (92.0)	26 (81.3)	7 (100.0)	133 (89.3)
Failure	4 (11.4)	6 (8.0)	6 (18.8)	0 (0.0)	16 (10.7)

Age groups are based on actual age, therefore some patients are represented in multiple columns.
A successfully treated bleed is a bleeding episode where the treatment response was excellent or good.

Table 11: Actual consumption of nonacog beta pegol - full analysis set

	Younger children (0-6 years)	Older children (7-12 years)	Total
Number of patients	12	13	25
Consumption used for treatment* per year per patient** (IU/kg/year)			
N	12	13	25
Mean (SD)	2235.7 (79.2)	2288.7 (127.5)	2263.2 (108.3)
Median	2259.1	2300.2	2261.5
Min ; Max	2015.1 ; 2300.9	2031.4 ; 2516.8	2015.1 ; 2516.8
Average prophylaxis dose*** (IU/kg)			
N	4952	4504	9456
Mean (SD)	43.1 (1.8)	43.2 (1.5)	43.2 (1.7)
Median	43.0	43.2	43.1
Min ; Max	14.3 ; 56.0	6.4 ; 49.2	6.4 ; 56.0
Average dose for minor surgery*** (IU/kg)			
N	9	5	14
Mean (SD)	42.1 (1.9)	47.9 (7.8)	44.1 (5.4)
Median	41.7	45.1	42.7
Min ; Max	40.5 ; 46.5	42.7 ; 61.5	40.5 ; 61.5
Average dose for major surgery*** (IU/kg)			
N	2	0	2
Mean (SD)	41.8 (0.0)	- (-)	41.8 (0.0)
Median	41.8	-	41.8
Min ; Max	41.8 ; 41.8	- ; -	41.8 ; 41.8
Average dose for treatment of bleed from start to stop of bleed+ (IU/kg/bleed)			
N	63	86	149
Mean (SD)	51.0 (25.8)	64.4 (70.8)	58.7 (56.6)
Median	42.7	43.5	43.2
Min ; Max	21.9 ; 213.4	26.7 ; 569.3	21.9 ; 569.3
Number of days between doses***++			
N	4940	4491	9431
Mean (SD)	7.1 (0.8)	7.1 (1.6)	7.1 (1.2)
Median	7.0	7.0	7.0
Min ; Max	1.0 ; 23.0	1.0 ; 65.0	1.0 ; 65.0
Frequency of doses in/out of compliance***+++, N (%)			
N	4940 (100.0)	4491 (100.0)	9431 (100.0)
6-8 days	4873 (98.6)	4211 (93.8)	9084 (96.3)
<6 days	16 (0.3)	104 (2.3)	120 (1.3)
>8 days	51 (1.0)	176 (3.9)	227 (2.4)

SD: standard deviation
*Consumption used for treatment includes all doses given (prophylaxis, treatment of bleed, minor and major surgery and PK)
**N is number of patients
***N is number of doses
+N is number of bleeds
++Only count prophylaxis doses except the first prophylaxis dose
+++Out of compliance is defined as a prophylaxis dose given less than 6 days or more than 8 days since last prophylaxis dose

Table 12: Number of injections of nonacog beta pegol per bleed - full analysis set

	Younger children (0-6 years)	Older children (7-12 years)	Total
Number of patients	12	13	25
Number of patients with bleeds, N (%)	9 (75.0)	12 (92.3)	21 (84.0)
Number of patients with 0 bleeds, N(%)	3 (25.0)	1 (7.7)	4 (16.0)
Number of bleeds	63	86	149
Number of injections to treat the bleed*, N (%)			
N	63 (100.0)	86 (100.0)	149 (100.0)
1 injection	54 (85.7)	69 (80.2)	123 (82.6)
2 injections	8 (12.7)	9 (10.5)	17 (11.4)
3 injections	-	5 (5.8)	5 (3.4)
5 injections	1 (1.6)	-	1 (0.7)
7 injections	-	2 (2.3)	2 (1.3)
12 injections	-	1 (1.2)	1 (0.7)
N	63	86	149
Mean (SD)	1.2 (0.6)	1.5 (1.5)	1.4 (1.2)
Median	1.0	1.0	1.0
Min ; Max	1.0 ; 5.0	1.0 ; 12.0	1.0 ; 12.0

*N is number of bleeds. SD: standard deviation.

Table 13: Detail of bleeds - full analysis set

	Younger children (0-6 years)	Older children (7-12 years)	Total
Number of patients	12	13	25
Number of patients with bleeds, N(%)	9 (75.0)	12 (92.3)	21 (84.0)
Number of patients with 0 bleeds, N(%)	3 (25.0)	1 (7.7)	4 (16.0)
Number of bleeds	63	86	149
Cause of bleed, N (%)			
N	63 (100.0)	86 (100.0)	149 (100.0)
Spontaneous	11 (17.5)	34 (39.5)	45 (30.2)
Traumatic	51 (81.0)	48 (55.8)	99 (66.4)
After minor surgery	1 (1.6)	-	1 (0.7)
Other	-	4 (4.7)	4 (2.7)
Re-bleed, N (%)			
N	63 (100.0)	86 (100.0)	149 (100.0)
Yes	1 (1.6)	2 (2.3)	3 (2.0)
No	62 (98.4)	84 (97.7)	146 (98.0)
Location of bleed, N (%)			
N	63 (100.0)	84 (100.0)	147 (100.0)
Joint	24 (38.1)	38 (45.2)	62 (42.2)
C.N.S.	1 (1.6)	-	1 (0.7)
Muscular	4 (6.3)	21 (25.0)	25 (17.0)
Subcutaneous	14 (22.2)	4 (4.8)	18 (12.2)
Skin	6 (9.5)	-	6 (4.1)
Gastrointestinal	-	1 (1.2)	1 (0.7)
Mucosal	8 (12.7)	10 (11.9)	18 (12.2)
Urinary system	-	2 (2.4)	2 (1.4)
Other	6 (9.5)	8 (9.5)	14 (9.5)
Location of bleed and cause, N (%)			
N	63 (100.0)	84 (100.0)	147 (100.0)
Joint, spontaneous	1 (1.6)	19 (22.6)	20 (13.6)
Joint, traumatic	22 (34.9)	19 (22.6)	41 (27.9)
Joint, after minor surgery	1 (1.6)	-	1 (0.7)
C.N.S., traumatic	1 (1.6)	-	1 (0.7)
Muscular, spontaneous	2 (3.2)	5 (6.0)	7 (4.8)
Muscular, traumatic	2 (3.2)	16 (19.0)	18 (12.2)
Subcutaneous, spontaneous	3 (4.8)	-	3 (2.0)
Subcutaneous, traumatic	11 (17.5)	4 (4.8)	15 (10.2)
Skin, traumatic	6 (9.5)	-	6 (4.1)
Gastrointestinal, traumatic	-	1 (1.2)	1 (0.7)
Mucosal, spontaneous	4 (6.3)	4 (4.8)	8 (5.4)
Mucosal, traumatic	4 (6.3)	2 (2.4)	6 (4.1)
Mucosal, other	-	4 (4.8)	4 (2.7)
Urinary system, spontaneous	-	1 (1.2)	1 (0.7)
Urinary system, traumatic	-	1 (1.2)	1 (0.7)
Other, spontaneous	1 (1.6)	5 (6.0)	6 (4.1)
Other, traumatic	5 (7.9)	3 (3.6)	8 (5.4)
Classification of bleed, N (%)			
N	63 (100.0)	86 (100.0)	149 (100.0)
Mild/moderate	63 (100.0)	86 (100.0)	149 (100.0)
Time of onset of bleed**, N (%)			
N	62 (100.0)	75 (100.0)	137 (100.0)
From 7 a.m. to 11 a.m.	11 (17.7)	22 (29.3)	33 (24.1)
From 11 a.m. to 3 p.m.	14 (22.6)	15 (20.0)	29 (21.2)
From 3 p.m. to 7 p.m.	15 (24.2)	21 (28.0)	36 (26.3)
From 7 p.m. to 11 p.m.	12 (19.4)	15 (20.0)	27 (19.7)
From 11 p.m. to 3 a.m.	8 (12.9)	1 (1.3)	9 (6.6)
From 3 a.m. to 7 a.m.	2 (3.2)	1 (1.3)	3 (2.2)
Time of onset of bleed and cause**, N (%)			
N	62 (100.0)	75 (100.0)	137 (100.0)
From 7 a.m. to 11 a.m., spontaneous	4 (6.5)	10 (13.3)	14 (10.2)
From 7 a.m. to 11 a.m., traumatic	6 (9.7)	12 (16.0)	18 (13.1)
From 7 a.m. to 11 a.m., after minor surgery	1 (1.6)	-	1 (0.7)
From 11 a.m. to 3 p.m., spontaneous	1 (1.6)	6 (8.0)	7 (5.1)
From 11 a.m. to 3 p.m., traumatic	13 (21.0)	9 (12.0)	22 (16.1)
From 3 p.m. to 7 p.m., spontaneous	-	9 (12.0)	9 (6.6)
From 3 p.m. to 7 p.m., traumatic	15 (24.2)	12 (16.0)	27 (19.7)
From 7 p.m. to 11 p.m., spontaneous	2 (3.2)	7 (9.3)	9 (6.6)
From 7 p.m. to 11 p.m., traumatic	10 (16.1)	8 (10.7)	18 (13.1)
From 11 p.m. to 3 a.m., spontaneous	2 (3.2)	-	2 (1.5)
From 11 p.m. to 3 a.m., traumatic	6 (9.7)	1 (1.3)	7 (5.1)
From 3 a.m. to 7 a.m., spontaneous	2 (3.2)	1 (1.3)	3 (2.2)
Time since last dose**, N (%)			
N	59 (100.0)	74 (100.0)	133 (100.0)
<=4 days	26 (44.1)	37 (50.0)	63 (47.4)
>4 days	33 (55.9)	37 (50.0)	70 (52.6)
Time since last dose and cause**, N (%)			
N	59 (100.0)	74 (100.0)	133 (100.0)
<=4 days, after minor surgery	1 (1.7)	-	1 (0.8)
<=4 days, spontaneous	4 (6.8)	14 (18.9)	18 (13.5)
<=4 days, traumatic	21 (35.6)	23 (31.1)	44 (33.1)
>4 days, spontaneous	5 (8.5)	18 (24.3)	23 (17.3)
>4 days, traumatic	28 (47.5)	19 (25.7)	47 (35.3)

C.N.S: Central nervous system.
Duration is only calculated if both start and stop time of bleed is reported.
Only primary location is summarised
**Only calculated if complete time points are available

Table 14: Duration of bleeds - full analysis set

	Younger children (0-6 years)	Older children (7-12 years)	Total
Number of patients	12	13	25
Number of patients with bleeds, N(%)	9 (75.0)	12 (92.3)	21 (84.0)
Number of patients with 0 bleeds, N(%)	3 (25.0)	1 (7.7)	4 (16.0)
Number of bleeds	63	86	149
Duration of bleed (hours)			
N	57	65	122
Mean (SD)	49.1 (100.3)	67.7 (90.9)	59.0 (95.4)
Median	17.7	34.6	24.9
Min ; Max	0.2 ; 666.3	1.4 ; 471.0	0.2 ; 666.3
Time from bleed onset to first dose (hours)			
N	62	73	135
Mean (SD)	8.6 (26.9)	12.5 (21.0)	10.7 (23.9)
Median	2.0	3.1	2.3
Min ; Max	0.0 ; 198.3	0.0 ; 94.3	0.0 ; 198.3
Time from first dose to stop of bleed (hours)			
N	57	66	123
Mean (SD)	39.9 (93.7)	58.6 (84.8)	49.9 (89.2)
Median	12.0	20.8	17.7
Min ; Max	0.0 ; 665.5	0.5 ; 379.3	0.0 ; 665.5

Duration and time in relation to onset, dose and stop is only calculated if complete time points are available.
SD: standard deviation.

Table 15: Major surgery - full analysis set

Patient ID/Age(yrs) /Treatment	Description of surgery	Indication	Surgery start datetime/ Surgery end datetime	Impf	Datetime of preventive dose	Haemostatic response
[redacted] /Prophylaxis 40 IU/kg	Arteriovenous fistula closure	Fistula closure because venous access is now available	[redacted]:12:10:00/ :13:00:00		[redacted]:11:27	EXCELLENT

Table 16: Minor surgery - full analysis set

Patient ID/Age(yrs) /Treatment	Description of surgery	Indication	Surgery start datetime/ Surgery end datetime	Impf	Datetime of preventive dose	Haemostatic response
[redacted] /Prophylaxis 40 IU/kg	Port a cath removal	non-functional port-a-cath, no longer needed	[redacted] 11:54:00/ 12:42:00		[redacted] 10:54	
[redacted] /Prophylaxis 40 IU/kg	Extraction of teeth [redacted] and [redacted]	Impacted supernumerary teeth	[redacted] 13:15:00/ 13:33:00		[redacted] 11:22	
	Dental extractions involving two regular teeth and one supranumerary tooth that will require an incision.	supranumerary tooth	[redacted] 12:00:00/ 23:59:00	H/ H	[redacted] 07:45	
[redacted] /Prophylaxis 40 IU/kg	right orchidopexy	right, unilateral cryptorchidism	[redacted] 14:42:00/ 15:11:00		[redacted] 14:11	
[redacted] /Prophylaxis 40 IU/kg	Extraction of [redacted] [redacted]molar)	Exfoliation	[redacted] 15:00:00/ 15:35:00		[redacted] 14:22	
[redacted] /Prophylaxis 40 IU/kg	Bronchoscopy	Haemoptysis for investigation	[redacted] 09:50:00/ 10:00:00		[redacted] 08:00	
[redacted] /Prophylaxis 40 IU/kg	tooth extraction	baby tooth removal	[redacted] 14:00:00/ 14:30:00			
	removal of 2 teeth	teeth removal	[redacted] 10:00:00/ 12:00:00		[redacted] 07:45	
[redacted] /Prophylaxis 40 IU/kg	Correction of nasal deviation	Fractured nose	[redacted] 16:29:00/ 16:56:00		[redacted] 12:08	
[redacted] /Prophylaxis 40 IU/kg	Tooth removed	Abscess tooth	[redacted] 14:45:00/ 15:00:00		[redacted] 12:00	
[redacted] /Prophylaxis 40 IU/kg	Myringotomy and grommet insertion	Glue ear	[redacted] 10:00:00/ 10:23:00		[redacted] 09:30	
[redacted] /Prophylaxis 40 IU/kg	Portacath removal	Infected portacath	[redacted] 12:00:00/ 00:00:00	H/	[redacted] --:--	
	PortaCath insertion	To infuse regular clotting factor	[redacted] 12:00:00/ 00:00:00	H/	[redacted] --:--	
	Grommets	[redacted] ear infection	[redacted] 12:00:00/ 00:00:00	H/	[redacted] --:--	
[redacted] /Prophylaxis 40 IU/kg	Open Reduction and Internal fixation, [redacted]	fracture of [redacted]	[redacted] 09:00:00/ 12:00:00		[redacted] 07:00	
	pin removal surgery	fracture of [redacted]	[redacted] 09:00:00/ 10:00:00			
[redacted] /Prophylaxis 40 IU/kg	Deciduous tooth extraction	Deciduous tooth extraction	[redacted] 15:52:00/ 16:16:00			
	Deciduous tooth extraction	Deciduous tooth extraction	[redacted] 17:00:00/ 17:00:00			
	Deciduous tooth extraction gingival flap excision	Deciduous tooth extraction gingival flap excision	[redacted] 15:50:00/ 16:00:00 [redacted] 15:50:00/ 16:30:00			
	Pulpectomy	Pulpectomy	[redacted] 13:00:00/ 13:13:00			
[redacted] /Prophylaxis 40 IU/kg	Tooth extraction	Baby tooth removal	[redacted] 10:00:00/ 10:45:00			

Impf: Date time imputation flag, H if time is imputed

Patient reported outcomes and health economic endpoints

Haemophilia -quality of life (HAEMO-QOL)

HAEMO-QOL scores range from a 0 to 100 scale where high scores (nearing 100) indicate a low quality of life rating. Questionnaires were distributed to patients (4-7 years, 8-12 years) and parents of patients at the screening visit of the trial, at end of main phase and visit 17. A new age fitted PRO questionnaire was introduced at visit 17 and served as baseline data for visits 24, 25, 26, 27, 28 and end of trial. Only a few patients responded to questionnaires at visit 24 (3 patients), visit 25 (2 patients), visit 26 (3 patients), visit 27 (1 patient), visit 28 (1 patient), end of trial (2 patients).

At visit 1, the observed mean HAEMO-QOL was:

- 4.8 score units for patients aged 4-7 years
- 31.7 score units for patients aged 8-12 years

At visit 1, the observed mean HAEMO-QOL was:

- 12.2 score units for parents of children aged 4-7 years
- 30.3 score units for parents of children aged 8-12 years

At visit 17, the observed mean change in HAEMO-QOL was:

- 2.0 score units for patients aged 4-7 years
- -11.4 score units for patients aged 8-12 years

At visit 17, the observed mean change in HAEMO-QOL was:

- 4.3 score units for parents of children aged 4-7 years
- -9.5 score units for parents of children aged 8-12 years

Table 17: Health economic aspects - full analysis set

	Younger children (0-6 years)	Older children (7-12 years)	Total
Number of patients	12	13	25
Number of general hospitalisation days, N (%)			
N	4 (100.0)	5 (100.0)	9 (100.0)
0	3 (75.0)	5 (100.0)	8 (88.9)
1	1 (25.0)	-	1 (11.1)
Number of intensive care hospitalisation days			
N	4	5	9
Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Median	0.0	0.0	0.0
Min ; Max	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0
Number of days bleedings caused missing school or studies, N (%)			
N	11 (100.0)	13 (100.0)	24 (100.0)
0	9 (81.8)	11 (84.6)	20 (83.3)
1	1 (9.1)	-	1 (4.2)
2	1 (9.1)	2 (15.4)	3 (12.5)
Number of days using mobility aids			
N	11	13	24
Mean (SD)	0.4 (0.7)	1.0 (3.3)	0.7 (2.5)
Median	0.0	0.0	0.0
Min ; Max	0.0 ; 2.0	0.0 ; 12.0	0.0 ; 12.0
Number of days bleedings caused parents to miss work			
N	11	13	24
Mean (SD)	0.3 (0.6)	0.5 (0.9)	0.4 (0.8)
Median	0.0	0.0	0.0
Min ; Max	0.0 ; 2.0	0.0 ; 2.0	0.0 ; 2.0

Pharmacokinetics

Pharmacokinetic endpoints, except FIX trough and FIX activity at 30 minutes (C30min) after reached steady state, were assessed after a single dose (Visit 2). Steady state trough and C30min were assessed at Visit 4 - Visit 10 during the main phase of the trial. Pre-dose FIX activity was analysed until LPLV.

Endpoints were:

- Incremental recovery at 30 minutes (IR30min) ([IU/mL] / [IU/kg])
- Area under the curve (AUC) (Uxh/mL)
- Terminal half-life (t1/2) (h)

- Clearance (CL) (mL/h/kg)
- Mean residence time (MRT) (h)
- Volume of distribution at steady state (Vss) (mL/kg)
- FIX activity at 30 minutes (C30min) (IU/mL) (single-dose)
- Trough level (IU/mL) (single-dose)

Table 18: Analysis of FIX trough levels, one-stage clotting assay by actual age groups - full analysis set

	Younger children (0 - 6 years)	Older children (7 - 12 years)	Adolescents (13-17 years)	Adult (18-70 years)	Total
Number of patients	12	23	14	6	25
Number of trough values included in the analysis*	126	243	97	14	480
Number of trough values excluded from the analysis*	6	13	30	19	68
Number of values below lower limit of quantification**	0	0	0	0	0
Mixed model results***					
Mean trough level (IU/mL)	0.146	0.193	0.220	0.316	0.186
95% CI	0.127 ; 0.166	0.171 ; 0.218	0.192 ; 0.252	0.254 ; 0.394	0.165 ; 0.210

* Trough values prior visit 4 are not included.
To be included in the analysis, measurements must have been taken at least 5 days and no more than 10 days after last dose, as well as at least 14 days after last bleeding episode.
** Plasma activities below lower limit of quantification (LLOQ) of 0.01 IU/mL are set to half of LLOQ (0.005 IU/mL).
*** The analysis is based on a mixed model on the log-transformed plasma concentrations with patient as a random effect. The mean trough level is presented back-transformed to the natural scale.
Age groups are based on actual age, therefore some patients are represented in multiple columns.

Safety results

Adverse events

The safety evaluation is based on 25 patients exposed to nonacog beta pegol. Given the long duration of the combined main and extension phase, there were 14 patients who became adolescents (13-17 year age group) and 6 patients became adults (18-70 year age group) at some point during the extension phase.

Table 19: Overview of adverse events by actual age group - safety analysis set

	Younger children (0 - 6 years) N (%) E [R]	Older children (7 - 12 years) N (%) E [R]	Adolescents (13 - 17 years) N (%) E [R]	Adults (18 - 70 years) N (%) E [R]	Total N (%) E [R]
Number of patients	12	23	14	6	25
Total time in trial (years)	34.20	81.50	53.43	15.31	184.44
Total number of exposure days	1815	4294	2798	758	9665
All adverse events	11 (91.7) 252 [7.37]	20 (87.0) 342 [4.20]	12 (85.7) 81 [1.52]	4 (66.7) 10 [0.65]	24 (96.0) 685 [3.71]
Serious adverse events	2 (16.7) 3 [0.09]	4 (17.4) 5 [0.06]	1 (7.1) 1 [0.02]	-	7 (28.0) 9 [0.05]
Medical event of special interest	1 (8.3) 1 [0.03]	3 (13.0) 3 [0.04]	4 (28.6) 5 [0.09]	1 (16.7) 1 [0.07]	7 (28.0) 10 [0.05]
Adverse events by severity					
Mild	11 (91.7) 221 [6.46]	20 (87.0) 313 [3.84]	10 (71.4) 69 [1.29]	3 (50.0) 7 [0.46]	24 (96.0) 610 [3.31]
Moderate	5 (41.7) 29 [0.85]	10 (43.5) 29 [0.36]	8 (57.1) 11 [0.21]	2 (33.3) 3 [0.20]	17 (68.0) 72 [0.39]
Severe	1 (8.3) 2 [0.06]	-	1 (7.1) 1 [0.02]	-	2 (8.0) 3 [0.02]
Adverse events by relationship					
Probably or possibly related	1 (8.3) 2 [0.06]	4 (17.4) 7 [0.09]	-	1 (16.7) 1 [0.07]	6 (24.0) 10 [0.05]
Unlikely related	11 (91.7) 250 [7.31]	20 (87.0) 335 [4.11]	12 (85.7) 81 [1.52]	4 (66.7) 9 [0.59]	24 (96.0) 675 [3.66]
Missing	-	-	-	-	-
Adverse events					
Leading to withdrawal	-	-	-	-	-

All adverse events in this table are treatment emergent.
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/total time in trial).
Age groups are based on actual age, therefore some patients are represented in multiple columns.
MedDRA version 26.1.
Relationship to trial product is evaluated by the investigator.

Table 20: Adverse events with possible or probable relation to trial product by actual age groups – safety analysis set

	Younger children (0 - 6 years) N (%) E [R]	Older children (7 - 12 years) N (%) E [R]	Adolescents (13 - 17 years) N (%) E [R]	Adults (18 - 70 years) N (%) E [R]	Total N (%) E [R]
Number of patients	12	23	14	6	25
Total time in trial (years)	34.20	81.50	53.43	15.31	184.44
Total number of exposure days	1815	4294	2798	758	9665
All adverse events	1 (8.3) 2 [0.06]	4 (17.4) 7 [0.09]	-	1 (16.7) 1 [0.07]	6 (24.0) 10 [0.05]
Gastrointestinal disorders	1 (8.3) 2 [0.06]	1 (4.3) 1 [0.01]	-	-	2 (8.0) 3 [0.02]
Abdominal pain	1 (8.3) 1 [0.03]	-	-	-	1 (4.0) 1 [0.01]
Diarrhoea	1 (8.3) 1 [0.03]	-	-	-	1 (4.0) 1 [0.01]
Nausea	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [0.01]
General disorders and administration site conditions	-	2 (8.7) 3 [0.04]	-	-	2 (8.0) 3 [0.02]
Infusion site pain	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [0.01]
Injection site pain	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [0.01]
Injection site reaction	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [0.01]
Blood and lymphatic system disorders	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [0.01]
Eosinophilia	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [0.01]
Ear and labyrinth disorders	-	-	-	1 (16.7) 1 [0.07]	1 (4.0) 1 [0.01]
Hypoacusis	-	-	-	1 (16.7) 1 [0.07]	1 (4.0) 1 [0.01]
Nervous system disorders	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [0.01]
Headache	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [0.01]
Respiratory, thoracic and mediastinal disorders	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [0.01]
Wheezing	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [0.01]

All adverse events in this table are treatment emergent.
Relationship to trial product is evaluated by the investigator.
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/total time in trial).
Age groups are based on actual age, therefore some patients are represented in multiple columns.
MedDRA version 26.1.

Serious adverse events

Table 21: Serious adverse events by actual age groups - safety analysis set

	Younger children (0 - 6 years) N (%) E [R]	Older children (7 - 12 years) N (%) E [R]	Adolescents (13 - 17 years) N (%) E [R]	Adults (18 - 70 years) N (%) E [R]	Total N (%) E [R]
Number of patients	12	23	14	6	25
Total time in trial (years)	34.20	81.50	53.43	15.31	184.44
Total number of exposure days	1815	4294	2798	758	9665
All adverse events	2 (16.7) 3 [0.09]	4 (17.4) 5 [0.06]	1 (7.1) 1 [0.02]	-	7 (28.0) 9 [0.05]
Infections and infestations	1 (8.3) 2 [0.06]	1 (4.3) 1 [0.01]	-	-	2 (8.0) 3 [0.02]
Catheter site infection	1 (8.3) 1 [0.03]	-)	-	-	1 (4.0) 1 [0.01]
Gastroenteritis viral	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [0.01]
Viral upper respiratory tract infection	1 (8.3) 1 [0.03]	-	-	-	1 (4.0) 1 [0.01]
Congenital, familial and genetic disorders	1 (8.3) 1 [0.03]	1 (4.3) 1 [0.01]	-	-	2 (8.0) 2 [0.01]
Cryptorchism	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [0.01]
Tourette's disorder	1 (8.3) 1 [0.03]	-	-	-	1 (4.0) 1 [0.01]
Gastrointestinal disorders	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [0.01]
Food poisoning	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [0.01]
Injury, poisoning and procedural complications	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [0.01]
Radius fracture	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [0.01]
Nervous system disorders	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [0.01]
Migraine	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [0.01]
Respiratory, thoracic and mediastinal disorders	-	-	1 (7.1) 1 [0.02]	-	1 (4.0) 1 [0.01]
Haemoptysis	-	-	1 (7.1) 1 [0.02]	-	1 (4.0) 1 [0.01]

All adverse events in this table are treatment emergent.
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/total time in trial).
Age groups are based on actual age, therefore some patients are represented in multiple columns.

Deaths

No adverse events with fatal outcome were recorded.

Adverse events leading to withdrawal from the trial

No adverse event lead to withdrawal from the trial up to the data cut off point.

Medical events of special interest

Medical events that were predefined for this trial as being of special interest (MESI) for the safety evaluation were: CNS-related adverse events, allergic reactions, renal adverse events, embolic and thrombotic events, inhibitor formation against FIX, medication errors, anaphylactic reactions.

Table 22: Medical events of special interest (MESI) by actual age groups - safety analysis

	Younger children (0 - 6 years) N (%) E [R]	Older children (7 - 12 years) N (%) E [R]	Adolescents (13 - 17 years) N (%) E [R]	Adults (18 - 70 years) N (%) E [R]	Total N (%) E [R]
Number of patients	12	23	14	6	25
Total time in trial (years)	34.20	81.50	53.43	15.31	184.44
Total number of exposure days	1815	4294	2798	758	9665
Medical events of special interest	1 (8.3) 1 [0.03]	3 (13.0) 3 [0.04]	4 (28.6) 5 [0.09]	1 (16.7) 1 [0.07]	7 (28.0) 10 [0.05]
Allergic reactions	-	2 (8.7) 2 [0.03]	3 (21.4) 4 [0.08]	-	4 (16.0) 6 [0.03]
Urticaria	-	-	1 (7.1) 2 [0.04]	-	1 (4.0) 2 [0.01]
Allergy to arthropod bite	-	-	1 (7.1) 1 [0.02]	-	1 (4.0) 1 [0.01]
Miliaria	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [0.01]
Rhinitis allergic	-	-	1 (7.1) 1 [0.02]	-	1 (4.0) 1 [0.01]
Wheezing	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [0.01]
Central nervous system related events	1 (8.3) 1 [0.03]	-	1 (7.1) 1 [0.02]	1 (16.7) 1 [0.07]	3 (12.0) 3 [0.02]
Headache	-	-	1 (7.1) 1 [0.02]	-	1 (4.0) 1 [0.01]
Migraine	-	-	-	1 (16.7) 1 [0.07]	1 (4.0) 1 [0.01]
Tourette's disorder	1 (8.3) 1 [0.03]	-	-	-	1 (4.0) 1 [0.01]
Renal and urinary disorders	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [0.01]
Proteinuria	-	1 (4.3) 1 [0.01]	-	-	1 (4.0) 1 [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/total time in trial).
Age groups are based on actual age, therefore some patients are represented in multiple columns.
MedDRA version 26.1.

Medical events of special interest – Central nervous system related

The number of central nervous system related events during the on-treatment period was:

- 1 event in 1 (8.3%) patient (incidence rate 0.03 events per PYE) in the younger children (0-6 years) group
- 0 events the older children (7-12 years) group
- 1 event in 1 (7.1%) patient (incidence rate 0.02 events per PYE) in the adolescents (13-17 years) group
- 1 event in 1 (16.7%) patient (incidence rate 0.07 events per PYE) in the adults (18-70 years) group

The following numbers of events were serious:

- 1 event in 1 (8.3%) patient (incidence rate 0.03 events per PYE) in the younger children (0-6 years) group
- 0 events in the older children (7-12 years), adolescents (13-17 years) or adults (18-70 years) groups

Medical events of special interest – Allergy

The number of allergy events during the on-treatment period was:

- 0 events in the younger children (0-6 years) group
- 2 events in 2 (8.7%) patients (incidence rate 0.03 events per PYE) in the older children (7-12 years) group

- 4 events in 3 (21.4%) patients (incidence rate 0.08 events per PYE) in the adolescents (13-17 years) group
- 0 events in the adults (18-70 years) group

None of the events was serious

Medical events of special interest - Renal events

Renal events were pre-defined as MESIs for this trial and were identified with a MedDRA search.

The number of renal events during the on-treatment period was:

- 0 events in the younger children (0-6 years) group
- 1 event in 1 (4.3%) patient (incidence rate 0.01 events per PYE) in the older children (7-12 years) group
- 0 events in the adolescents (13-17 years) group
- 0 events in the adults (18-70 years) group

None of the events was serious

Medical events of special interest – Embolic and thrombotic events

No embolic and thrombotic event was reported during the on-treatment period.

Medical events of special interest – FIX inhibitors

No FIX inhibitor event was reported during the on-treatment period.

Medical events of special interest – Medication errors

No medication errors was reported during the on-treatment period.

Medical events of special interest – Anaphylactic reaction

No anaphylactic reaction was reported during the on-treatment period.

Clinical laboratory evaluation

Biochemistry

No clinically relevant findings were observed for the biochemistry parameters during the trial.

Figure 1: Mean profiles of eGFR (mL/min) – safety analysis set

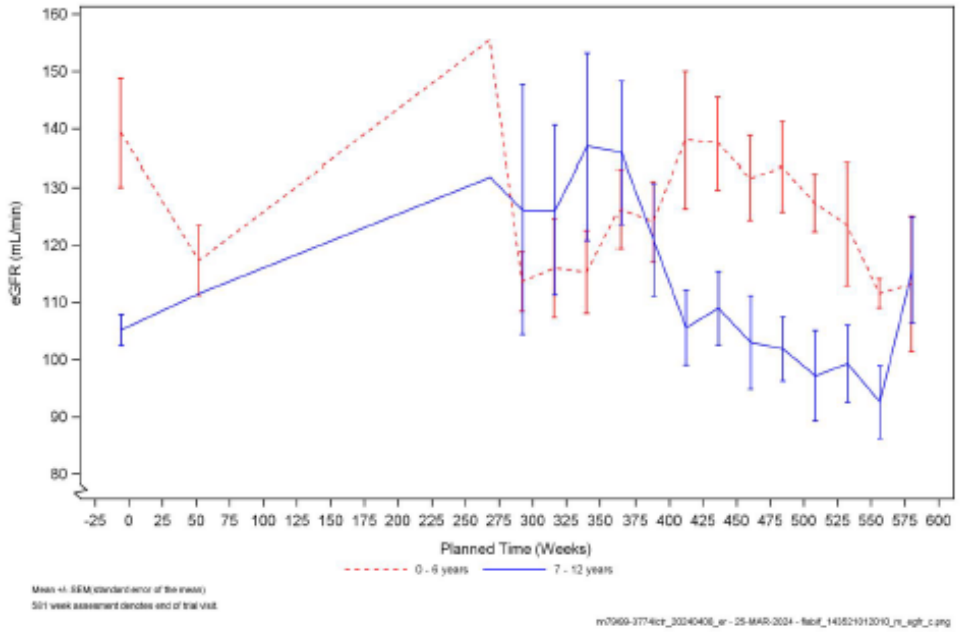
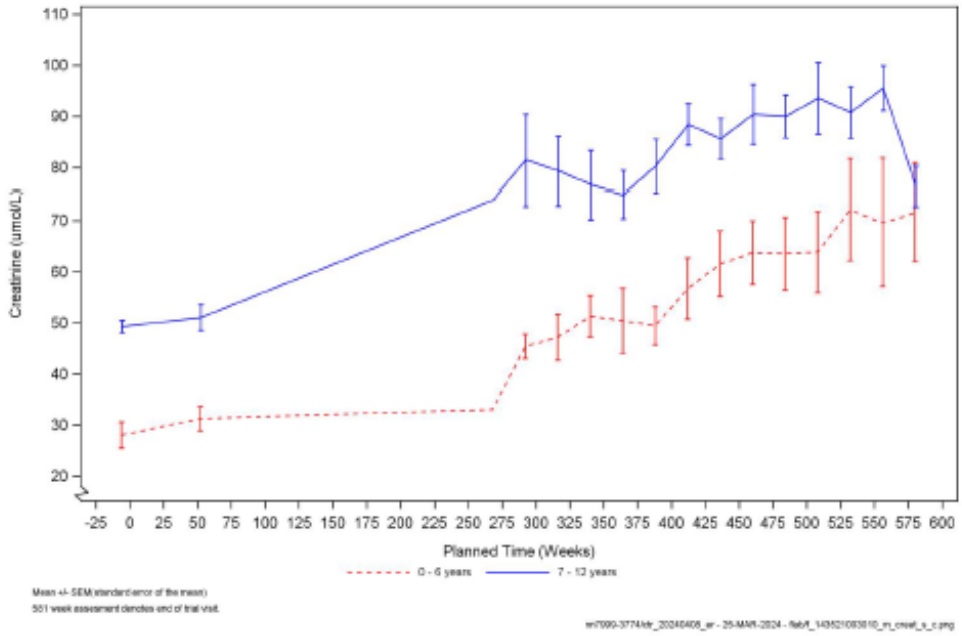


Figure 2: Mean profiles of creatinine (µmol/L) – safety analysis set



Haematology

No clinically relevant findings were observed for the haematology parameters during the trial.

PEG plasma concentration

At the end of trial, the observed mean (SD) PEG concentration was:

- 5.8 (1.95) µg/mL for patients in the younger children (0-6 years) group
- 5.6 (2.36) µg/mL for patients in the older children (7-12 years) group

Figure 3: PEG - individual profiles of full profile PEG plasma concentration (ug/mL) - safety analysis set

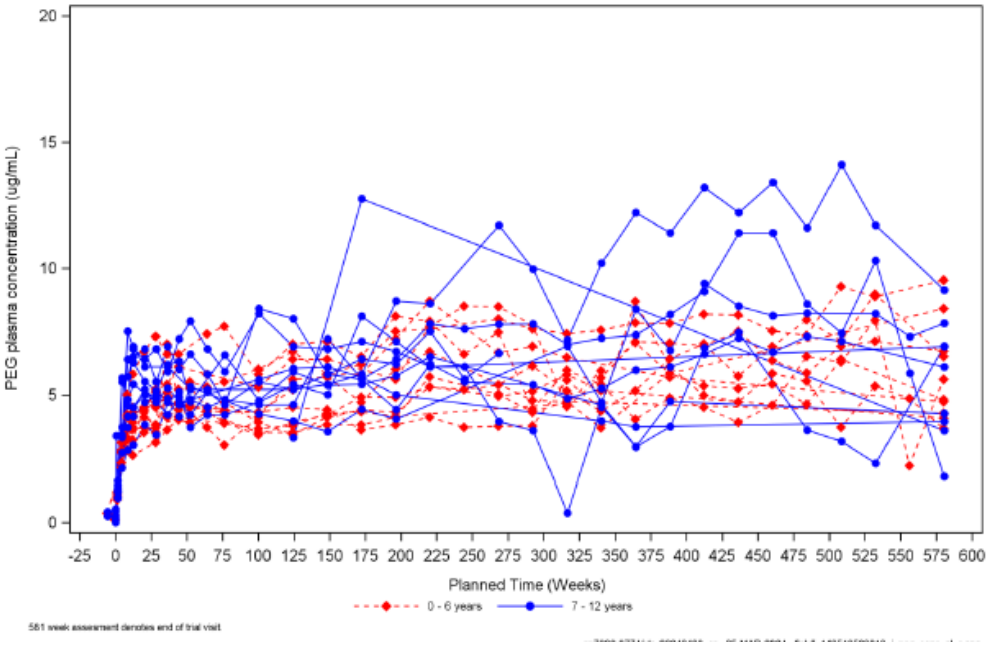
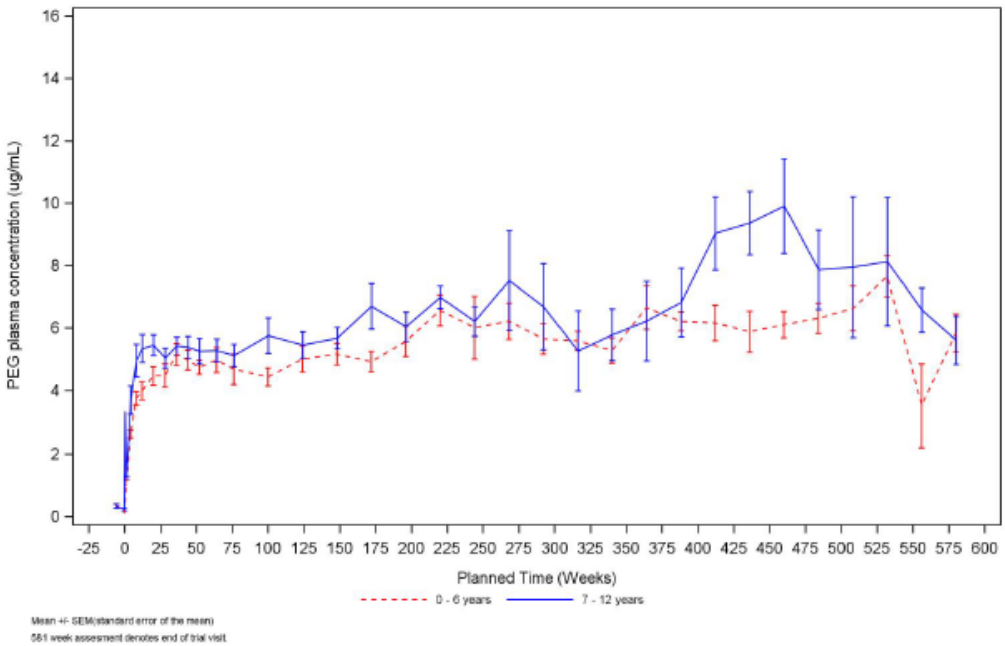


Figure 4: PEG - mean profiles of full profile PEG plasma concentration (ug/mL) - safety analysis set



Vital signs

No clinically relevant findings were observed for vital signs.

Physical examination

No clinically relevant findings were observed for the physical examination parameters during the trial.

Body measurements

No clinically relevant findings were observed for the body measurement parameters during the trial.

Pregnancy

There were no pregnancies of patients reported in the trial.

Antibodies

Primary endpoint – Incidence of inhibitory antibodies against FIX

The number of patients having inhibitory antibodies against FIX at any point during the on treatment period was:

0 in the younger children (0-6 years) group

0 in the older children (7-12 years) group

Table 23: Incidence of inhibitory antibodies against FIX - safety analysis set

	Younger children (0 - 6 years)	Older children (7 - 12 years)	Total
Number of patients	12	13	25
Number of patients with inhibitory antibodies*	0	0	0
Number of patients at risk**	12	13	25
Rate of inhibitory antibodies***			
Estimated inhibitor rate	0	0	0
1-sided 97.5% upper confidence limit	0.31	0.29	0.16

The inhibitor antibodies was measured using a Nijmegen modified FIX Bethesda assay or heat/cold Nijmegen modified FIX Bethesda assay.
* All patients with neutralising antibodies are included in the numerator.
** Any patient with a minimum 10 exposure days plus any patient with acquired inhibitory antibodies is included in the denominator.
*** Estimates are based on exact calculations for a binomial distribution.

Evaluation of neurological examinations and neurocognitive assessments

Neurological examination results

Age-appropriate neurological examinations were included with protocol amendment 9, version 2.0 in the extension phase of the trial in December 2017. Patients were examined every 6 months in the extension phase of the trial. The inherent parameters were: general, cranial nerves, coordination and fine motor functioning, reflexes, sensory, gait, strength and tone.

No clinically relevant findings were observed for neurological examination.

Figure 5: Shifts in neurological examination - general - safety analysis set

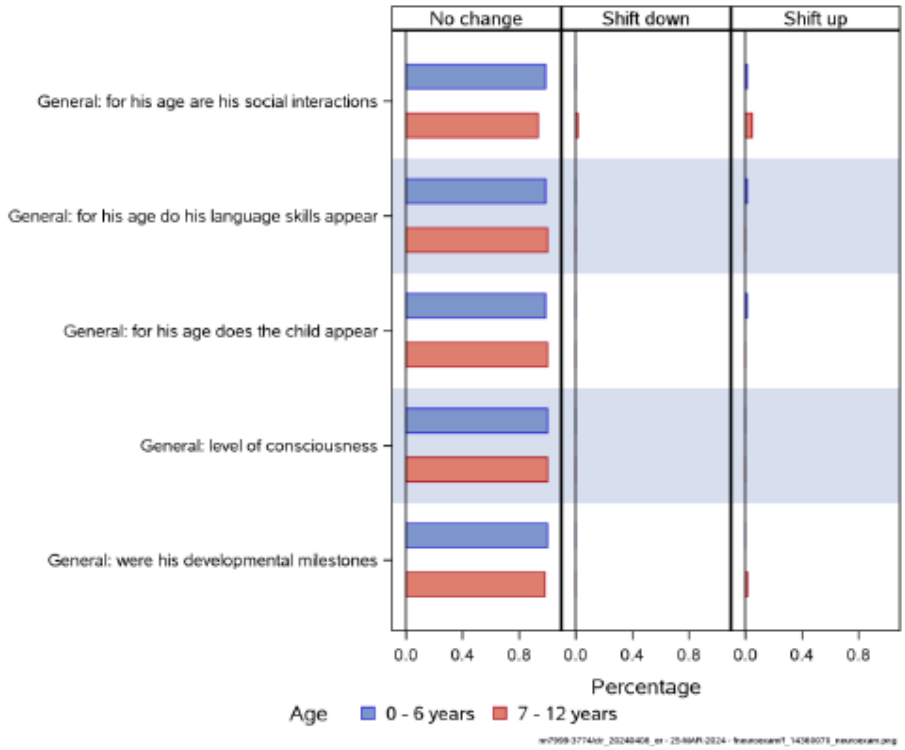


Figure 6: Shifts in neurological examination - cranial nerves - safety analysis set

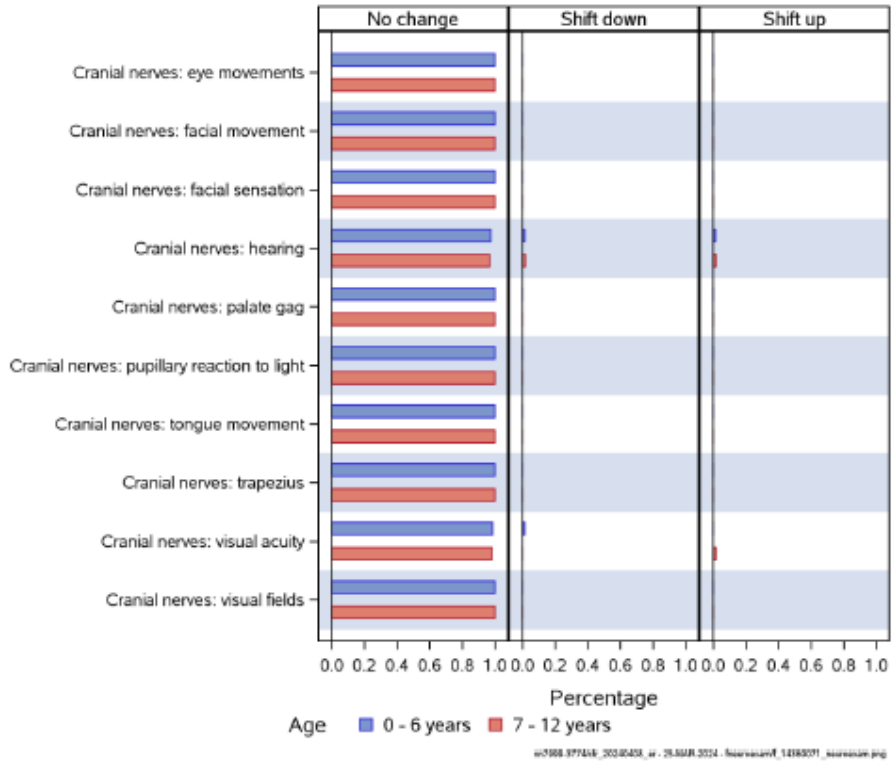


Figure 7: Shifts in neurological examination - coordination and fine motor, reflexes and sensory – safety analysis set

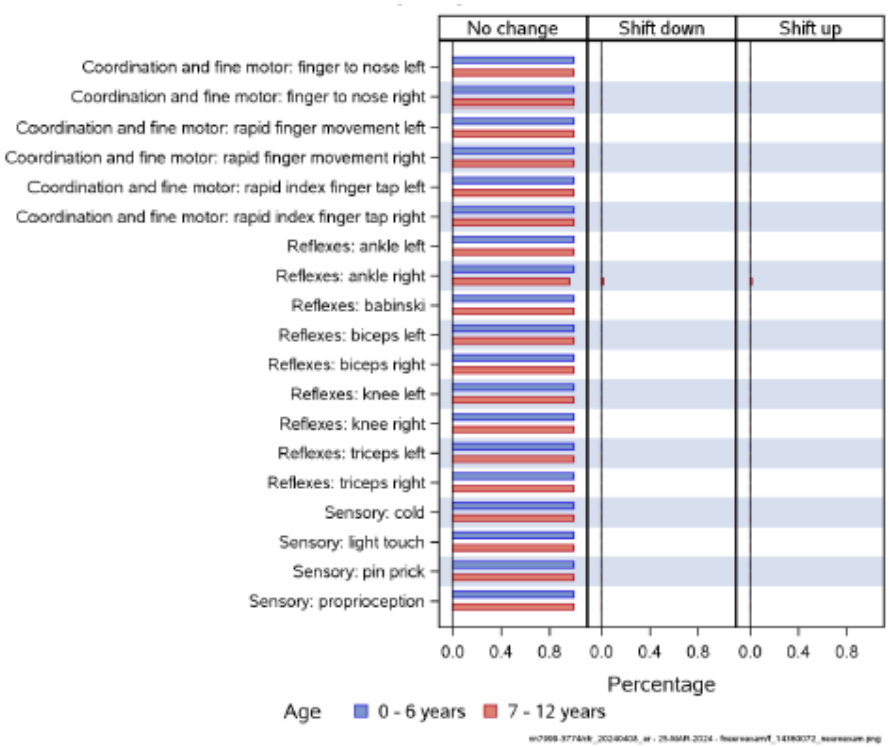


Figure 8: Shifts in neurological examination - gait, strength and tone - safety analysis set

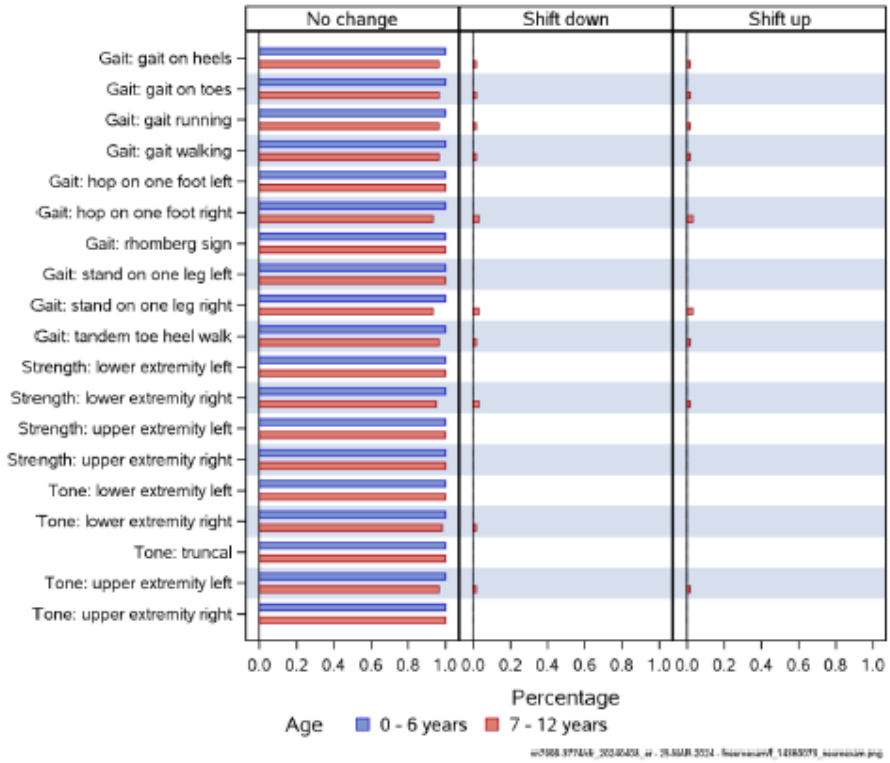


Table 24: Shifts in neurological examinations - by domain - safety analysis set

Domain		Total N	No change N (%)	Shift down N (%)	Shift up N (%)
General	For his age does the child appear	141	140 (99.29)	0 (0.0)	1 (0.71)
	For his age do his language skills appear	141	140 (99.29)	0 (0.0)	1 (0.71)
	For his age are his social interactions	141	136 (96.45)	1 (0.71)	4 (2.84)
	Were his developmental milestones	141	140 (99.29)	0 (0.0)	1 (0.71)
	Level of consciousness	141	141 (100.00)	0 (0.0)	0 (0.0)
Cranial nerves	Pupillary reaction to light	141	141 (100.00)	0 (0.0)	0 (0.0)
	Visual fields	140	140 (100.00)	0 (0.0)	0 (0.0)
	Visual acuity	139	137 (98.56)	1 (0.72)	1 (0.72)
	Eye movements	141	141 (100.00)	0 (0.0)	0 (0.0)
	Facial sensation	141	141 (100.00)	0 (0.0)	0 (0.0)
	Facial movement	141	141 (100.00)	0 (0.0)	0 (0.0)
	Hearing	141	137 (97.16)	2 (1.42)	2 (1.42)
	Palate gag	137	137 (100.00)	0 (0.0)	0 (0.0)
	Tongue movement	140	140 (100.00)	0 (0.0)	0 (0.0)
	Trapezius	141	141 (100.00)	0 (0.0)	0 (0.0)
Tone	Truncal	141	141 (100.00)	0 (0.0)	0 (0.0)
	Upper extremity left	141	139 (98.58)	1 (0.71)	1 (0.71)
	Upper extremity right	141	141 (100.00)	0 (0.0)	0 (0.0)
	Lower extremity left	139	139 (100.00)	0 (0.0)	0 (0.0)
	Lower extremity right	139	138 (99.28)	1 (0.72)	0 (0.0)
Strength	Upper extremity left	141	141 (100.00)	0 (0.0)	0 (0.0)
	Upper extremity right	141	141 (100.00)	0 (0.0)	0 (0.0)
	Lower extremity left	140	140 (100.00)	0 (0.0)	0 (0.0)
	Lower extremity right	140	137 (97.86)	2 (1.43)	1 (0.71)
Reflexes	Biceps left	141	141 (100.00)	0 (0.0)	0 (0.0)
	Biceps right	140	140 (100.00)	0 (0.0)	0 (0.0)
	Triceps left	140	140 (100.00)	0 (0.0)	0 (0.0)
	Triceps right	140	140 (100.00)	0 (0.0)	0 (0.0)
	Knee left	140	140 (100.00)	0 (0.0)	0 (0.0)
	Knee right	140	140 (100.00)	0 (0.0)	0 (0.0)
	Ankle left	139	139 (100.00)	0 (0.0)	0 (0.0)
	Ankle right	139	137 (98.56)	1 (0.72)	1 (0.72)
Reflexes	Babinski	135	135 (100.00)	0 (0.0)	0 (0.0)
Sensory	Cold	136	136 (100.00)	0 (0.0)	0 (0.0)
	Pin prick	137	137 (100.00)	0 (0.0)	0 (0.0)
	Light touch	140	140 (100.00)	0 (0.0)	0 (0.0)
	Proprioception	137	137 (100.00)	0 (0.0)	0 (0.0)
Gait	Gait walking	140	138 (98.57)	1 (0.71)	1 (0.71)
	Gait running	137	135 (98.54)	1 (0.73)	1 (0.73)
	Gait on heels	137	135 (98.54)	1 (0.73)	1 (0.73)
	Gait on toes	138	136 (98.55)	1 (0.72)	1 (0.72)
	Tandem toe heel walk	139	137 (98.56)	1 (0.72)	1 (0.72)
	Stand on one leg left	139	139 (100.00)	0 (0.0)	0 (0.0)
	Stand on one leg right	140	136 (97.14)	2 (1.43)	2 (1.43)
	Hop on one foot left	138	138 (100.00)	0 (0.0)	0 (0.0)
	Hop on one foot right	139	135 (97.12)	2 (1.44)	2 (1.44)
	Rhomberg sign	139	139 (100.00)	0 (0.0)	0 (0.0)
Coordination and fine motor	Finger to nose left	141	141 (100.00)	0 (0.0)	0 (0.0)
	Finger to nose right	141	141 (100.00)	0 (0.0)	0 (0.0)
	Rapid index finger tap left	137	137 (100.00)	0 (0.0)	0 (0.0)
	Rapid index finger tap right	137	137 (100.00)	0 (0.0)	0 (0.0)
	Rapid finger movement left	139	139 (100.00)	0 (0.0)	0 (0.0)
	Rapid finger movement right	139	139 (100.00)	0 (0.0)	0 (0.0)
Overall		7394	7354 (99.46)	18 (0.24)	22 (0.30)

N: number of shifts.
Shift is defined by change from previous exam: no change - normal to normal or abnormal to abnormal, shift down - normal to abnormal, shift up - abnormal to normal.

Neurocognitive assessments

Age-appropriate neurocognitive assessments (NCAs) were performed after implementation of protocol amendment 10 (27-June-2018). As the protocol amendment was implemented while the trial was ongoing, all initial NCAs were performed after exposure to nonacog beta pegol.

A set of comprehensive instruments to evaluate neurodevelopmental, neurocognitive and neuro behavioural function and development were used. Age-adjusted domain and composite scores for each neurocognitive instrument were calculated using available methods. The individual patient's overall/age-adjusted domain/sub-scores for each neurocognitive assessment instrument were expressed as an individual's z-score (i.e. an indication of how many standard deviations (SD) a domain score is from the mean) and compared against the general US population and the haemophilia normative data for children and young adults (HAEM- 4436, eTHINK study).

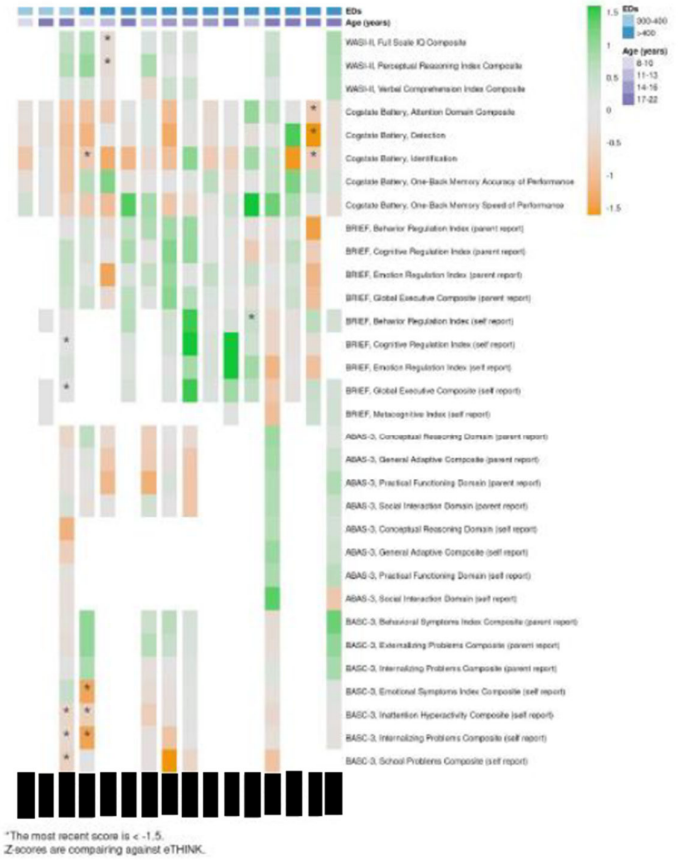
Below, individual patient z-score profiles are presented for each of the 5 instruments. The z-score represents the number of standard deviations a domain score is from the mean haemophilia normative data for children and young adults (HAEM-4436, eTHINK study. A z-score of -1.5 standard deviations versus the eTHINK study was defined as the clinical cut-off to identify potential clinical concern.

No clinically relevant findings were observed for Neurocognitive assessments results.

The Figure below is a graphical presentation of NCA data using color-coding to represent values of interest. For each individual patient, orange colour represents a decrease in z-scores (against eTHINK) and green colour represents an increase. The figure depicts the change from initial to subsequent NCA for all 5 instruments versus exposure days and patient age. If ≥3 NCAs were available, then the mean of the change from initial to each of the subsequent NCAs is included in the heatmap. Note that patients with only 1 assessment for an instrument are not displayed in the heatmap.

The association between z-scores for BRIEF and Cogstate battery and exposure was analysed using a random regression model. The statistical analysis for change over time in composite z-scores for BRIEF parent and self-reports and Cogstate battery is shown in the following Table.

Figure 9: Mean change in Z-scores from initial assessment for primary outcome measures - safety analysis set



*The most recent score is < -1.5.
Z-scores are compairing against eTHINK.

Table 25: Statistical analysis of Z-scores - safety analysis set

Parameter	Fixed effect	Number of patients contributing to analysis	Number of assessments contributing to analysis	Estimate of coefficient	p-value
Global Executive Composite (parent report)	Exposure day	13	91	0.0017	0.116
Global Executive Composite (self report)	Exposure day	14	98	0.0016	0.316
Attention Domain Composite	Exposure day	16	126	0.0009	0.510

Z-scores are against eTHINK.
Based on a random regression model with exposure day as fixed effect and subject as random effect, allowing random intercept and random slope for exposure day for each individual subject.

Key conclusions of External Expert Review report

A summary report from each EERP meeting was prepared by Cogstate Ltd. Key conclusions from the report is provided below. Note that the term 'subsequent assessment' denotes the most recent assessment. Based on the available data, there do not appear to be specific consistent patterns of cognitive or behavioural decline in patients with or without clinical concern identified at initial assessment. Overall, the number of patients with initial clinical concern declined from 5 to 3 patients at subsequent visits assessed at Meeting 5. The number of patients with no initial yet subsequent clinical concern at Meeting 5 decreased to 2 patients, from prior 4 patients at Meetings 3 & 4.

Overall, the majority of patients evaluated were functioning within normal limits for age based on performance measures and rating scales at initial assessment. Only 3 (19%) patients of the total of 16 patients enrolled in paradigm5, with available neurocognitive data, demonstrated below cut-off cognitive (test based) performance in at least one domain at initial assessment, one of them in the 'no concern' group. All patients in the initial clinical concern group had significant contributing factors, consistent with and considered to explain the neurocognitive findings. Similarly, the 2 patients with subsequent clinical concern at Meeting 5, both had identified contributing factors. The most consistently administered instruments were test-based measures of attention (Cogstate), and this domain also yielded the most frequent clinical findings, yet also the highest variability between assessments. Within the initial clinical concern group with available subsequent visit data, 4 patients showed some decline in aspects of attention over time, and 2 (13% of total sample, 40% of clinical concern group) showed decline below clinical cut-off at end of trial in at least one attention domain, yet 3 remained or improved within normal limits. Again, all of these patients had contributing factors in their history. Within the subsequent clinical concern group, only one patient (6% of total sample, 25% of subsequent clinical concern group) presented downward patterns of performance on attention measures, below cut-off at Meeting 4, but rising to above average between Meeting 4 and Meeting 5. This patient had contributing factors in the history.

Overall, there has been a pattern of notable fluctuation in test-based attention performance over time. As noted in the previous report, one explanation could lie in variability of measurement that has been observed in the Cogstate battery, particularly when examining specific subscales versus composite scores (Attention Domain Composite). Inconsistency between classifications of clinical concern based on changes in performance on individual subtests from the Cogstate tests when standardized psychological tests remained stable suggests that variability in individual Cogstate subtests were due to methodological or noise factors and therefore are likely reflect false positive results. The normative data for various age groups for the measure could introduce another source of variation. Additionally, a possible explanation could be an increased rate of attention problems identified in children with hemophilia, as also observed in the eTHINK study that formed the basis to the paradigm trials. Within that context, variable performance and functioning is a hallmark feature of ADHD, and several patients had noted pre-existing attention concerns in their history. Further, there were only limited concerns for reported executive functions, primarily on self-report, with only one patient in the initial clinical concern group and one patient in the subsequent concern group below cut-off. Similarly, emotional

concerns were most prevalent on self-report measures, albeit again only in a handful of patients (2 in the initial concern, none in the subsequent concern group at end of trial), and this was in part explained by contributing factors. This is consistent with findings from the eTHINK study that demonstrates emotional concerns primarily endorsed on adolescent/young adult self-report. Adaptive skills were rated as largely within normal limits for patients with clinical concerns.

The neurologic examinations did once again not explain neurocognitive findings, with the vast majority rated as 'normal' at initial visit and remaining stable in nearly all participants across subsequent evaluations to date. Only one patient () in the clinical concern group had abnormal neurologic findings, which were almost entirely explainable by pre-existing psychiatric diagnoses or health conditions. One patient () in the subsequent clinical concern group at a prior meeting presented with prior vision issues which are now corrected with lenses, and no longer of concern. One patient () who presented with new onset high frequency hearing loss as the only abnormality at Meeting 4, no longer had these concerns at Meeting 5, with otherwise entirely normal neurocognitive function on tests and rating scales, and also contributing factors. Investigation of potential contributing factors including prenatal, birth, developmental, medical, neurologic, school, or family histories, did not reveal any significant differences in frequency between patients with or without clinical concern.

2.3.3. Discussion on clinical aspects

The MAH submitted the final study report of the open-label paediatric study 3774. The long-term treatment data followed 25 previously treated patients (PTPs) 0-12 years old (n=12 patients 0-6 years and n=13 patients 7-12 years old at the time of study enrolment). Data generated during the main phase of study 3774 were assessed during initial MAA in 2016. Furthermore, an interim analysis of this study (study report date 3rd of September 2021) with a mean total exposure period per patient of 6 years (range 0.2 – 8.1 years), and a mean of in total 317 exposure days per patient was submitted in the scope of a type II variation (EMEA/H/C/004178/II/0032), which concluded a positive benefit-risk balance for the treatment of paediatric patients. Thus, data of the interim report were already assessed including the respective update of the product information. The final study report as submitted for this P46 procedure (study report date 8th of May 2024) comprises a mean total exposure period per patient of 7.4 years (range 0.2 – 11.4 years) and a mean of in total 386.6 exposure days per patient. The substantially longer treatment period submitted with the final study report is acknowledged. Conclusions on clinical pharmacology, efficacy and safety are reiterated where in line with the data submitted from interim analyses and potential crucial differences between reports are specifically highlighted.

In total 25 patients were exposed to the study drug during the main phase, 22 subjects entered the extension study (n=11 patients 0-6 years and n=11 patients 7-12 years old) and 10 of these subjects remained in the study until study completion. Importantly, all of the withdrawn patients reported data for efficacy assessment and thus are part of the FAS (n=25 as per enrolled subjects for the study during main phase) and no patient withdrew from the extension study due to an adverse event. Evaluated numbers of subjects are in line with requirements as outlined in the guideline on recombinant FIX products (EMA/CHMP/BPWP/144552/2009 rev. 2 Corr. 1; i.e. at least 10 PTPs for each age category with >150 ED for subjects 6-12 and >50 ED for subjects 0-6 years). It is also in line with the respective guideline that all previously treated patients had a history of at least 50 EDs (mean=346.3 EDs) to other FIX products and were without history of inhibitors. It is noted that several of the subjects 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 became adolescent (n=14 became 13-17 years old) and adult (n=6 became ≥18 years old) during the trial.

During study course n=10 subjects contributed to both paediatric age categories (i.e. 0-6 years and 7-12 years old). All subjects included in trial 3774 had severe (factor IX level <1%) or moderately severe (factor IX level ≤2%) haemophilia B.

A dose of 40 IU/kg was used for on demand treatment (mild and moderate bleeds) as well as for prophylactic treatment once weekly. Only major surgeries and severe bleeds were planned to be treated with 80 IU/kg. A major protocol amendment was implemented, in order to change the initially planned patient tailored dosing to a fixed dose (i.e. 40 IU/kg once weekly) during the extension phase. Thus, no dose adjustment was applied between the main phase and extension phase of the study, which appears supported by efficacy results previously reported for the main phase (see EPAR). In line with the study plan, the mean (SD) prophylaxis dose during the study was 43.2 (1.7) IU/kg and 149 bleeds were treated with a median dose of 43.2 IU/kg/bleed.

In total 10 protocol amendments and 311 important protocol deviations are reported for the study. Reported protocol amendments appear acceptable with respect to study conduct. The number of important protocol deviations appears high, but deviations during the main study phase (see EPAR) are comparable to reported deviations in other Factor IX products in a comparable study duration. It is further understood that the very long study duration of the reported extension study does lead to an accumulation of deviations over time. Importantly, no patient was excluded from the FAS as none of the PDs had an overall impact on the trial conduct, subject safety or data interpretation.

Pharmacokinetics

Pharmacokinetic data on Factor IX activity after single exposure in paediatric patients were reported during initial MAA of Refixia and steady state Factor IX activity was reported in the subsequent extension of indication to include paediatric patients. The detailed discussion on both can be found in the respective EPARs. The MAH updated the reported Factor IX trough levels (measured by the one-stage clotting assay), which remain within the range of mild haemophilia between 0.05 and 0.4 IU/mL (total estimated mean level was 0.146 IU/mL and 0.195 IU/mL for patients 0-6 years and 7-12 years old, respectively). Thus, the conclusion that prophylactic dosing of 40 IU/kg once a week appears to provide stable and sufficiently high trough levels for paediatric previously treated patients (≤12 years) remains valid. The recommended dosing in paediatric patients is supported by PK data on Factor IX activity during prophylactic dosing with nonacog beta pegol.

Efficacy

The evaluation of immunogenicity was the primary aim of study 3774. Efficacy, pharmacokinetics and further safety measures were evaluated as secondary objectives. The focus on immunogenicity in paediatric trials as well as the reported efficacy endpoints (e.g. bleeding rate, haemostatic response and Factor IX consumption) are acknowledged and well in line with data provided for other Factor IX products. Results presented for study 3774 do not indicate any reduction in efficacy for the long-term treatment (main + extension phase) compared to data reported for the main phase. Also, key efficacy results (details of bleeds, annualised bleeding rate, haemostatic response and consumption) presented separately for the main and extension phase do not indicate any loss of efficacy during the extension phase compared to results from the main phase.

Efficacy results appear principally in line with other Factor IX products with prolonged half-life that are licensed for paediatric subjects and no substantial variations were identified compared to the interim data that were assessed in the scope of the prior extension of indication.

The Poisson estimated ABR was 0.81 (95%CI: 0.5; 1.31) for all enrolled patients, and was 1.02 (95%CI: 0.68; 1.54) for younger children (0-6 years) and 0.92 (95%CI: 0.47; 1.78) for older children (7-12 years) when considering the actual age group (i.e. the paediatric age group that subjects

belonged to while they were exposed and assessed for efficacy with n=12 younger children and n=23 older children).

The haemostatic success rate was around 90% in paediatric subjects based on actual age (88.6% for 0-6 year old and 93.2% for 7-12 year old PTPs) and treatment failure was reported for 9 bleeds in this age categories (4 in 0-6 year old and 5 in 7-12 year old patients, from a total of 109 bleeds). Poor treatment outcome is noted for two bleeds (both in one patient <6 years), all other failures were rated with moderate response. Only 3 bleeds required >2 injections (twice 3 and once 5 injections). Similarly, the success rate regardless of age (i.e. also considering patients once they became older than 12 years) was 89.9% with 15 treatment failures in 148 bleeds. None of the breakthrough bleeding events in paediatric PTPs was rated as a severe bleeding event (all mild or moderate). With the previously assessed interim study report no new target joint had developed and two pre-existing target joints (both in patients 7-12 at the time of enrolment) had resolved during the main phase of the trial. However, with the final study data one patient developed a new target joint (age 13-17 years). One CNS bleed (extracranial) occurred throughout the study in a patient aged 0-6 years with an excellent haemostatic response. The CNS bleed was reported already in the interim report and no additional CNS bleed is reported in the final study report.

The median prophylactic dose used (43.1 IU/kg across all age groups) as well as the median dose required to treat and stop bleeding events (43.2 IU/kg across age groups) is in line with the recommended dose during the study (i.e. 40 IU/kg). This indicates the need for a single dose to treat the majority of bleeds (82.6%) and is in line with results discussed in the scope of the prior licensure of the treatment of paediatric patients. More than 2 injections to stop a breakthrough bleed were required in 6.1% of bleeds, which is slightly more compared to the 3% reported in the interim report.

The mean annual consumption of 2263.2 IU/kg in PTPs ≤12 years is comparable to other Factor IX products with prolonged half-life and in line with data reported in the interim report. The median duration of bleeds was 24.9 h (ranging from 0.2 to 666.3 h) and the median time from first dose to stop of bleed was 17.7 h (ranging from 0 to 665.5 h), both in line with data reported in the interim report.

A single major surgery in a -year-old subjects was performed (arteriovenous fistula closure) with a reported excellent haemostatic response after following the recommended dosing of 80 IU/kg (2 identical doses of 41.8 IU/kg were given). Furthermore, minor surgeries were performed in 12 subjects ≤12 years with a mean dose level of 44.1 IU/kg. The applied dose level was in line with the recommendation for preventive doses before surgeries. The haemostatic response to prophylactic treatment for minor surgeries was not recorded during study 3774.

As discussed for the interim report, the evaluation of PROs of treatment with N9-GP appear compromised by low patient numbers that contributed to these measures (2 patients at end of trial) no reliable statement can be provided regarding these aspects. Health economic aspects support other conclusions regarding efficacy, as most patients (83.3%) did not miss any days at school due to bleeds, no intensive care hospitalisation was reported and parents missed on average 0.4 days due to bleeding of a child.

Safety

Nonacog beta pegol is licensed in the EU since 2017 for the treatment and prophylaxis of bleeding in patients with haemophilia B aged 12 years and above. Due to non-clinical findings of PEG accumulation in certain tissues and ensuing concerns about the long-term safety of the PEG moiety (e.g. renal, hepatic and CNS-related adverse events), Refixia was not authorised in the whole paediatric population. With the approved extension of indication to include also paediatric patients ≤12 years, the MAH has provided an extensive investigation of the safety of long-term treatment with nonacog beta

pegol on paediatric patients with exposure times up to 8 years from trial 3774 interim analyses. The adverse event profile was concluded as consistent with expectations for the age group and with the profile observed in the already authorised population >12 years of age. The investigation of neurological, neurocognitive and neurobehavioural parameters specifically constructed to address possible effects of PEG accumulation was considered comprehensive and did not conclude any relevant influence of PEG on neurological development and function during long-term treatment with nonacog beta pegol. Please refer to the respective EPAR for more details. For the now submitted final study report the mean total number of exposure days is exceptionally high with 386.6 days (419.5 days in 0-6 year old and 356.2 days in 7-13 year old PTPs) and is in line with the used mean number of 387 doses per patient (in the interim report it was a mean exposure of 317 days with mean 317.3 doses per patient). The total number of exposure days increased from 3944 reported in the interim report to 4294 days (total years increased from 74.73 to 81.5). The number of exposed paediatric subjects surpasses guideline requirements and the duration of exposure is considered exceptional.

The number of reported AEs increased respectively with the increased number of exposure days (from 309 AEs in 20 patients in the latest assessed interim report to 342 events in 20 patients in the final study report). However, the events were considered unrelated to the study treatment for the majority of patients with AEs (87%), none of the events was severe and none led to withdrawal. Furthermore, none of the events with possible or probable relation appear concerning with respect to possible effects of PEG accumulation and all PTs were reported only once (2 events in 1 patient in 0-6 year old patients: PTs abdominal pain and diarrhoea, and 7 events in 4 7-12 year old patients: PTs nausea, infusion site pain, injection site pain, injection site reaction, eosinophilia, headache and weening).

In total 5 serious AEs in 4 patients 7-12 years old are reported for the final study report. Besides the previously described events from the study interim analysis, 2 additional serious events were noted, PTs cryptorchism and migraine. No additional SAE was reported for the final report compared to the interim report in PTPs 0-6 years of age (3 events in 2 patients). All PTs categorised as SAE were reported only once. It is also reassuring that no adverse events with fatal outcome were reported for paediatric PTPs.

The PEG plasma concentration at the end of trial 3774 at week 581 is reported with 5.8 (SD: 1.95) and 5.6 (SD: 2.36) µg/mL for younger children and older children, respectively. This concentration is in line with the plasma concentration time profile reported for the interim study analysis with values reaching a ceiling effect around 5-6 µg/mL after approximately 20 -30 weeks treatment with nonacog beta pegol, with the older age cohort displaying slightly higher levels. For the interim analysis PEG plasma levels were reported up to around 400 weeks. However, a substantial increase in plasma PEG levels is reported for older children from around week 400 (visit 27) until approximately week 525 (visit 33) with levels above or around 9 µg/mL until week 450 (visit 29) and 8 µg/mL until week 525. After week 525 levels seem to "normalise" to around 6 µg/mL. This temporal elevation in plasma levels is evident for older children only, mean plasma levels in younger children did not show such substantial increase, but rather a light elevation at visit 32 followed by a decline in plasma levels at visit 33. Reasons for the increased levels in older children are not discussed, but the effect seems to be particularly driven by 2 patients with levels >10 µg/mL. For one of these two patients (: peak PEG level at 14.1 µg/mL at visit 31) a low eGFR was evident at a single visit (77 mL/min at visit 31) without AE. The GFR had normalised at the following visit already, without treatment interruption. The other patient (: peak PEG level 11.4 µg/mL at visits 28 and 29) had a normal eGFR, but an adverse event of mild right renal dysfunction (not rate as MESI, as it happened before the respective protocol amendment that defined this categorization). The event was unresolved, considered unrelated and the patient continued to receive nonacog beta pegol without further AEs. As noted before, the clinical significance of plasma PEG levels is unknown at present. Furthermore, the increase was temporally restricted and mean PEG levels settled back to around 6 µg/mL at the end of the study, indicating that PEG does not further

accumulate in the plasma. Accumulation rates in other tissues are uncertain. Interestingly, also the mean estimated GFR in older children dropped around the same time as plasma PEG levels seemed elevated, from around 135 mL/min at visit 25 to 92.5 mL/min at visit 33. At the end of trial visit the eGFR was around 115 mL/min. Fluctuations in plasma levels and estimated GFR of both age groups could be related to the sparse patient numbers that were analysed for the respective measure for some of the visits. However, similarly sparse patient numbers were also seen for other visits that did not show the plasma level increase or reduction in eGFR. The fluctuation in eGFR as such does not appear critical as observed, but the coincidence with elevated PEG plasma levels in the age group is noted, considering that renal safety was in particular focus regarding possible PEG accumulation. No specific safety concern is raised as causalities still appear rather speculative, but it is noted that the two patients with highest PEG plasma levels between visit 27 and 33 had either a measure of low eGFR or an unresolved adverse event of renal dysfunction. A steady increase in creatinine levels was observed for both age groups, which however appears to be in the range of the expected age-related increase.

The extent of shifts in the neurological examination (up or down) appear comparable to data reported for the interim report. Also, the individual plots of neurocognitive measures as well as the mean change in z-scores across the neurocognitive examinations do not indicate any critical difference compared to the interim report, which is further supported by the statistical analysis of z-scores that do not indicate any statistically significant difference of neurocognitive measures compared to eTHINK (i.e. a standard population of haemophilia patients). Thus, conclusions regarding neurological and neurocognitive measures remain as provided in the prior assessment of interim data.

No patient developed inhibitory antibodies against Factor IX during the study. One subject developed anti-nonacog beta pegol antibodies without inhibitory effect. The patient continued the trial and tested negative for these antibodies at later visits. One paediatric subjects tested positive for anti-CHO antibodies and negative at subsequent visits. This is the same immunogenicity profile as reported at the interim analysis. No concern arises with regard to immunogenicity in paediatric PTPs.

3. Rapporteur’s overall conclusion and recommendation

The assessment of the long-term safety profile indicates a rather benign safety profile of nonacog beta profile, which underlines the conclusions derived from the interim study data. However, an elevation in mean PEG plasma levels was noted in later visits beyond the previous interim report. It is noted that the two patients with highest PEG plasma levels in this period had either a measure of low eGFR or an unresolved adverse event of renal dysfunction, but no specific safety concern is raised as causalities still appear rather speculative. The benefit-risk profile of nonacog beta pegol remains positive for PTPs ≤12 years as concluded in the prior extension of indication to include paediatric patients in the label.

☒ **Fulfilled:**

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. In the final study report (8th of May 2024) a single event of migraine was reported for a patient 7-12 years old as serious event, but a single event of migraine was also reported as medical event of special interest in a patient 13-17 years old (and none in other age groups). In the interim report of study 3774 (3rd of September 2021) migraine was reported as medical

event of special interest in an adult patient, but not as serious AE. The correct allocation of this event appears currently unclear. As migraine is of special interest from neurological perspective, the Applicant is asked to clarify the allocation of this event and to correct the respective information in the final CSR if necessary.

2. The Applicant is asked to discuss possible reasons for increase in PEG plasma levels and the temporally coinciding drop in eGFR around the late study visits 27 and 33, also considering a possible relation of both events. In line with this, individual PEG levels should be compared to individual eGFR values of the same patient and any possible coincidence with AEs and/or variations in other laboratory data (e.g. creatinine) should be discussed.

The timetable is a 30 day response timetable with clock stop.

5. MAH responses to Request for supplementary information

Question 1

In the final study report (8th of May 2024) a single event of migraine was reported for a patient 7-12 years old as serious event, but a single event of migraine was also reported as medical event of special interest in a patient 13-17 years old (and none in other age groups). In the interim report of study 3774 (3rd of September 2021) migraine was reported as medical event of special interest in an adult patient, but not as serious AE. The correct allocation of this event appears currently unclear. As migraine is of special interest from neurological perspective, the Applicant is asked to clarify the allocation of this event and to correct the respective information in the final CSR if necessary.

MAH Response

Novo Nordisk acknowledges the assessor’s comment regarding the discrepancy in the reporting of the adverse event ‘migraine’. This event of migraine was recorded as serious adverse event (SAE) (rather than medical event of special interest [MESI]) in one patient (ID:) and as MESI in another patient (ID:). For patient (ID:), the event of migraine was resolved on and the patient had not reported with any further events of migraine. Both patients continued to receive nonacog beta pegol. Details of these 2 patients with AE onset date, number of exposure days (EDs) at onset of adverse event (AE) and resolution date are captured in the Table 1 below.

For patient , the event of migraine was reported as an SAE by investigator during the trial and the same event was not marked as MESI. Consequently, in the table, figure and listings (TFL), the event of migraine was classified as an SAE based on the information collected on the case report form (CRF) and Novo Nordisk as sponsor does not advise changing the investigator's reported data. However, Novo Nordisk has an internal process to address discrepancies and errors in clinical trial reporting, though this error does not have any impact on the overall conclusion of the trial reported in the CSR. This process ensures that any errors identified after the final Clinical Study Report (CSR) is issued are documented and addressed without altering the original investigator-reported data. The key steps in this process include:

- **Identification of Errors**: Any discrepancies or errors in the clinical trial data are identified during the review process or through feedback from assessors.
- **Documentation**: These errors are documented in a CSR post-final issue log. This log captures details such as the nature of the error, the affected data points, and the potential impact on the overall trial conclusions.

- **Assessment**: The errors are assessed to determine if they have any substantial impact on the trial's conclusions. If the errors are deemed non-substantial, they are documented without requiring amendments to the final CSR.
- **Filing**: The CSR post-final issue log is filed internally to ensure that the errors are recorded and can be referenced in the future if needed.
- **Communication**: Relevant stakeholders are informed about the errors and the steps taken to address them. This ensures transparency and maintains the integrity of the trial data.

This process allows Novo Nordisk to maintain accurate and consistent reporting while ensuring that any identified errors are properly documented and addressed.

As per the above steps involved in the internal process, we have now documented this error in a CSR post final issue log. This is considered as a non-substantial change and therefore, an amendment to the final CSR is not required.

Table 1 Adverse events – Trial 3774

Trial 3774	Age at onset of AE	Onset date/resolution date	EDs at onset of event	SOC/PT	MESI	SAE	Severity/relationship	Action/Outcome
[redacted] (Final CSR dated 08 May 2024)	[redacted] years	[redacted]	412	Nervous system disorders/Migraine	No	Yes	Mild/unlikely	Dose not changed/Recovering[a]
[redacted] (Ext-2 [dated 03 Sep 2021] and Final CSRs)	[redacted]	[redacted]	415	Nervous system disorders/Migraine	Yes	No	Moderate/unlikely	Dose not changed/ Recovered

[a] The event was resolved on [redacted] and the patient had not reported with any further events of migraine.

AE = adverse event; CSR = clinical study report; EDs = exposure days; Ext = extension; MESI = medical event of special interest; PT = preferred term; SAE = serious adverse event; SOC = system organ class.

Assessment of Responses

The MAH has clarified that for the final study report one event of migraine was reported as SAE for a patient 7-12 years old and another event of migraine was regarded a medical event of special interest in an adult patient (not regarded a SAE).

Conclusion

Issue resolved.

Question 2

The Applicant is asked to discuss possible reasons for increase in PEG plasma levels and the temporally coinciding drop in eGFR around the late study visits 27 and 33, also considering a possible relation of both events. In line with this, individual PEG levels should be compared to individual eGFR values of the same patient and any possible coincidence with AEs and/or variations in other laboratory data (e.g. creatinine) should be discussed.

MAH Response

In trial 3774, the mean steady-state polyethylene glycol (PEG) plasma concentration ranged from 4.7-7.9 µg/mL. There were 16 patients with PEG plasma concentrations ranging from 1.76 to 14.1 µg/mL around the late visits 27 to visit 33. Of these 16 patients, 3 patients (patient IDs:, and) had PEG levels above the upper mean level of 7.9 µg/mL, and the nonacog beta pegol dose given for these patients from visit 27 to the end of trial (EoT) visit was in the range of 40.3-43.3 IU/kg (Table 2).

1. Patient : This patient experienced high PEG levels (9.14 to 14.1 µg/mL) and slightly decreased estimated glomerular filtration rate (eGFR) (77.05 mL/min, reference rage: <90 ml/min) at visit 31, accompanied by a slight increase in creatinine (112 umol/L, reference range: 60-105 umol/L [age group: 18 years and above]). Both eGFR and creatinine normalized at the subsequent visit, and no adverse events were reported. The patient continued to receive nonacog beta pegol and had high factor IX activity levels due to a high prophylactic dose administered the day prior to

sample collection. Elevated FIX activity levels resulted in high PEG levels. No adverse events have been reported for this patient. While eGFR values fluctuated between visits 27 and 32, they normalized again without any medical intervention.

2. Patient : This patient experienced elevated PEG levels (7.34 to 9.53 µg/mL) and a single measurement of elevated creatinine (97 umol/L) at the EoT visit (reference range: 52-93 umol/L [age group: 14-18 years]). The eGFR remained within normal values throughout the trial. The creatinine level normalized at the subsequent visits without any medical intervention, and no relevant adverse events were reported. The single measurement of slightly increased creatinine accompanied by normal eGFR is not considered as a safety concern.

3. Patient : This patient had PEG levels ranging from 5.84 to 11.4 µg/mL while eGFR remained normal. An adverse event of "renal impairment" (right renal dysfunction) was reported (Trial 3774-Final [M 5.3.5.2], Appendix 16.2.6, Listings 16.2.7), starting on . The event was mild, unresolved, and unlikely related to nonacog beta pegol by the investigator.

   No further information on this event is available. According to the protocol amendment version 9.0 (dated 01 December 2017) (Trial 3774-Final [M 5.3.5.2], Protocol amendment version 9.0), NovoNordisk agreed to monitor the potential CNS, renal and hepatic events and categorise them as MESIs. The occurrence of right renal dysfunction took place before this protocol amendment and was therefore not categorized as a MESI by the investigator. The patient continued to receive nonacog beta pegol, and no other adverse events related to renal function were reported for this patient.

Generally, eGFR and creatinine levels can fluctuate, and in all the mentioned cases, these fluctuations did not coincide with the reporting of any other adverse events. Overall, eGFR and creatinine levels normalized in all three patients during continued use of nonacog beta pegol, and thus this is not considered to raise any safety concerns regarding renal function.

Table 2 Individual laboratory measurements

Subject ID	Baseline age	Actual age	Visit	Visit date	PEG ug/mL	eGFR mL/min	dose IU/Kg	Creatinine umol/L	ALT IU/L	AST IU/L	FIX activity	AE Term
[redacted]	10	[redacted]	Visit 27	[redacted]	13.2	97.55854	42.4	93	17	21	0.855	
[redacted]	10	[redacted]	Visit 28	[redacted]	12.2	97.55854	42.7	93	10	13	0.789	
[redacted]	10	[redacted]	Visit 29	[redacted]	13.4	82.07654	43.3	107	12	16	0.926	
[redacted]	10	[redacted]	Visit 30	[redacted]	11.6	87.72858	42.6	101	17	17	0.391	
[redacted]	10	[redacted]	Visit 31	[redacted]	14.1	77.05632	42.3	112	11	14	0.848	
[redacted]	10	[redacted]	Visit 32	[redacted]	11.7	90.96436	42.8	97	11	14	0.871	
[redacted]	10	-	End of trial	[redacted]	9.14	93.39312	.	94	82	212	0.655	
[redacted]	5	[redacted]	Visit 27	[redacted]	8.18	129.5908	40.3	77	17	26	0.29	Dermatitis allergic
[redacted]	5	[redacted]	Visit 28	[redacted]	8.15	144.6576	42.5	70	16	25	0.327	
[redacted]	5	[redacted]	Visit 29	[redacted]	7.52	127.6558	42.1	77	14	28	0.306	
[redacted]	5	[redacted]	Visit 30	[redacted]	7.34	140.1841	42.5	71	11	21	0.26	
[redacted]	5	.	End of trial	[redacted]	9.53	95.17962	.	97	17	25	0.354	
[redacted]	9	[redacted]	Visit 27	[redacted]	9.08	90.76822	42.9	96	20	16	0.338	
[redacted]	9	[redacted]	Visit 28	[redacted]	11.4	98.69712	43	89	28	22	0.625	
[redacted]	9	[redacted]	Visit 29	[redacted]	11.4	92.90924	43	91	14	17	0.551	
[redacted]	9	[redacted]	Visit 30	[redacted]	8.58	90.76775	42	91	16	11	0.294	
[redacted]	9	[redacted]	Visit 31	[redacted]	7.43	94.04888	42.4	100	26	18	0.339	Hypoacusis
[redacted]	9	[redacted]	Visit 32	[redacted]	10.3	101.5154	42.4	93	32	21	0.571	Hypoacusis
[redacted]	9	[redacted]	Visit 33	[redacted]	5.84	98.94507	42	98	19	18	0.228	Hypoacusis
[redacted]	9	-	End of trial	[redacted]	1.76	97.92015	.	99	24	17	0.29	Hypoacusis

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate; FIX: factor IX; PEG: polyethylene glycol

Assessment of Responses

For the interim analysis PEG plasma levels were reported up to around 400 weeks. However, a substantial increase in plasma PEG levels is reported for older children from around week 400 (visit 27) until approximately week 525 (visit 33) with levels above or around 9 µg/mL until week 450 (visit 29) and 8 µg/mL until week 525. After week 525 levels seem to "normalise" to around 6 µg/mL. Reasons

for the increased levels in older children are not discussed, but the effect seems to be particularly driven by 2 patients with levels >10 µg/mL. For one of these two patients (: peak PEG level at 14.1 µg/mL at visit 31) a low eGFR was evident at a single visit (77 mL/min at visit 31) without AE. The GFR had normalised at the following visit already, without treatment interruption. The other patient (: peak PEG level 11.4 µg/mL at visits 28 and 29) had a normal eGFR, but an adverse event of mild right renal dysfunction (not rate as MESI, as it happened before the respective protocol amendment that defined this categorization). The event was unresolved, considered unrelated and the patient continued to receive nonacog beta pegol without further AEs. As noted before, the clinical significance of plasma PEG levels is unknown at present. Furthermore, the increase was temporally restricted and mean PEG levels settled back to around 6 µg/mL at the end of the study, indicating that PEG does not further accumulate in the plasma. Accumulation rates in other tissues are uncertain. Interestingly, also the mean estimated GFR in older children dropped around the same time as plasma PEG levels seemed elevated, from around 135 mL/min at visit 25 to 92.5 mL/min at visit 33. At the end of trial visit the eGFR was around 115 mL/min. Fluctuations in plasma levels and estimated GFR of both age groups could be related to the sparse patient numbers that were analysed for the respective measure for some of the visits. However, similarly sparse patient numbers were also seen for other visits that did not show the plasma level increase or reduction in eGFR. The fluctuation in eGFR as such does not appear critical as observed, but the coincidence with elevated PEG plasma levels in the age group is noted, considering that renal safety was in particular focus regarding possible PEG accumulation. No specific safety concern is raised as causalities still appear rather speculative, but it is noted that the two patients with highest PEG plasma levels between visit 27 and 33 had either a measure of low eGFR or an unresolved adverse event of renal dysfunction.

Conclusion

Issue resolved.

6. Rapporteur’s overall conclusion and recommendation

The assessment of the long-term safety profile indicates a rather benign safety profile of nonacog beta profile, which underlines the conclusions derived from the interim study data. However, an elevation in mean PEG plasma levels was noted in later visits beyond the previous interim report. It is noted that the two patients with highest PEG plasma levels in this period had either a measure of low eGFR or an unresolved adverse event of renal dysfunction, but no specific safety concern is raised as causalities still appear rather speculative. The benefit-risk profile of nonacog beta pegol remains positive for PTPs ≤12 years as concluded in the prior extension of indication to include paediatric patients in the label.

☒ **Fulfilled**