



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 June 2023
EMA/319611/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Refixia

International non-proprietary name: nonacog beta pegol

Procedure No. EMEA/H/C/004178/II/0032

Note

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



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List of abbreviations

aPTT activated partial thromboplastin time
ABR annualised bleeding rate
ADHD attention deficit hyperactivity disorder
AE adverse event
BU Bethesda unit
CHMP Committee for Medicinal Products for Human Use
CI confidence interval
CNS central nervous system
Cogstate Cogstate computerised battery
COVID-19 coronavirus disease 2019
C30min FIX activity 30 minutes post dosing
CT computed tomography
CTR clinical trial report
CSF cerebrospinal fluid
CVOs circumventricular organs
DBL database lock
DDD defined daily dose
DLP data lock point
ED exposure Day
EDC electronic data capture
EERP External Expert Review Panel
EMA European Medicines Agency
EU European Union
FFP fresh frozen plasma
FIX factor IX
eGFR estimated glomerular filtration rate
IR incremental recovery
IU international units
LLT lowest level term
MA marketing authorisation
MAA marketing authorisation application
MAH marketing authorisation holder
MESI medical event of special interest
N9-GP nonacog beta pegol
NN Novo Nordisk
PEG polyethylene glycol
PK pharmacokinetics
PRAC Pharmacovigilance Risk Assessment Committee
PRBC packed red blood cells
PSUR periodic safety assessment report
PT preferred term
PTP previously treated patient
PUP previously untreated patient
PYE patient-years of exposure
RMP risk management plan
RSI request for supplementary information
SAE serious adverse event
SmPC summary of product characteristics
SOC system organ class

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novo Nordisk A/S submitted to the European Medicines Agency on 30 November 2022 an application for a variation.

The following variation was requested:

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

Extension of indication to include treatment and prophylaxis of bleeding in children below 12 years of age with haemophilia B including previously untreated patients for REFIXIA based on results from studies NN7999-3774 and NN7999-3895. NN7999-3774 is a multicentre, open-label, non-controlled study evaluating the safety, efficacy and pharmacokinetics of nonacog beta pegol in previously treated children with haemophilia B, while NN7999-3895 is a multicentre, open-label, single-arm, non-controlled trial evaluating the safety and efficacy of nonacog beta pegol in previously untreated patients with haemophilia B. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated accordingly. Version 5.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI. The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0139/2019 on the agreement of a paediatric investigation plan (PIP).

The PDCO issued an opinion on compliance for the PIP P/0139/2019.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Timetable	Actual dates
Submission date	30 November 2022
Start of procedure:	31 December 2022
CHMP Rapporteur Assessment Report	24 February 2023
PRAC Rapporteur Assessment Report	3 March 2023
CHMP Co-Rapporteur Assessment	10 March 2023
PRAC members comments	8 March 2023
Updated PRAC Rapporteur Assessment Report	9 March 2023
PRAC Outcome	16 March 2023
CHMP members comments	20 March 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 March 2023
Request for supplementary information (RSI)	30 March 2023
CHMP Rapporteur Assessment Report	23 May 2023
PRAC members comments	31 May 2023
PRAC Outcome	8 June 2023
CHMP members comments	12 June 2023
Updated CHMP Rapporteur Assessment Report	15 June 2023
Opinion	22 June 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Haemophilia B is an X-linked recessive congenital bleeding disorder, caused by mutations in the genes encoding coagulation factor IX (FIX), with an incidence of approximately one in every 25,000 male births.

Signs and symptoms of haemophilia B are variable; depending on severity of the factor deficiency and the location of the bleeding. Thereby, bleeding is characterised by spontaneous or trauma-induced haemorrhage into joints, muscles and soft tissues. Severe haemophilia B is characterised by spontaneous or traumatic bleeding episodes into soft tissues and joints, but also life-threatening gastrointestinal or intracranial bleeding may occur. Recurrent joint bleeding may lead to chronic arthropathy and disability.

State the claimed the therapeutic indication

The MAH is submitting an extension of indication to include paediatric patients below 12 years of age as follows:

Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency). Refixia can be used for all age groups.

Management

The primary aim of care for patients with haemophilia B is to prevent bleeding which can successfully be managed with FIX replacement therapy. Replacement therapy with exogenous FIX provides a temporary correction of the coagulation factor deficiency by increasing FIX levels and thereby reducing bleeding.

Haemophilia B can successfully be managed with FIX replacement therapy. Besides of acute treatment of bleeding episodes, prophylactic treatment with the deficient clotting factor should be the goal of haemophilia therapy to preserve normal musculoskeletal function (World Federation of Haemophilia 2013). Therapeutic formulations of FIX are available as both plasma-derived FIX (pdFIX) and recombinant FIX (rFIX) products for treatment. Half-life of both pdFIX and rFIX is ~18 hours and prophylactic treatment is usually required 2 to 3 times a week in order to achieve a significant reduction of bleeding episodes. Several years ago, products with prolonged half-life such as Idelvion and Alprolix were approved. Hemgenix which is a gene therapy product has been authorised in 2023 for the treatment of severe and moderately severe Haemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors.

Development of neutralising anti-FIX antibodies (inhibitors) is a serious complication of FIX replacement therapy. Approximately 1-3% of all patients with haemophilia B develop inhibitors following exposure to FIX. Among patients with severe haemophilia B, the percentage is however as high as 9%. Most inhibitors develop in early childhood and after relatively few FIX exposure days. In patients who develop inhibitors to FIX, the condition will manifest itself as an insufficient clinical response to FIX replacement therapy. The occurrence of FIX inhibitors shows some correlation to allergic reactions, and patients with FIX inhibitors are at an increased risk of anaphylaxis with subsequent exposure to FIX.

2.1.2. About the product

Nonacog beta pegol is a recombinant human coagulation FIX product expressed in a genetically engineered Chinese hamster ovary cell line. A 40 kDa polyethylene glycol (PEG) moiety is attached to the FIX activation peptide by site-directed glycoPEGylation. PEGylation increases the half-life of the protein, and the prolonged circulation time is believed to arise from a reduction in the efficiency of various elimination processes such as renal excretion, receptor mediated uptake, and proteolytic degradation.

In the European Union (EU), the initial marketing authorisation for nonacog beta pegol (Refixia) was received on 02 June 2017 and indicated for treatment and prophylaxis of bleeding in patients aged 12 years and above with haemophilia B (congenital FIX deficiency).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

A positive PIP compliance check was issued by the PDCO on 15 November 2019. The development programme was conducted in accordance with scientific advice received from CHMP (EMA/H/SA/1297/4/2018/PED/III) and exceeding recommendations made at the time.

2.1.4. General comments on compliance with GLP, GCP

The MAH has assured the Rapporteur that all trials are carried out in compliance with GCP requirements.

2.2. Non-clinical aspects

2.2.1. Introduction

The non-clinical safety evaluation programme of nonacog beta pegol was originally designed in accordance with the guideline for biotechnology-derived pharmaceuticals provided by the International Conference of Harmonisation (ICH), ICH S6 R1, ICH M3 R2 and the European Medicine Agencies (EMA) Committee for Medicinal Products for Human Use (CHMP) Safety Working Party's (SWP) recommendation to the Paediatric Committee (PDCO) for use of PEGylated drugs in children. The original non-clinical program for nonacog beta pegol included primary pharmacodynamics, safety pharmacology, pharmacokinetics, distribution, metabolism, excretion, toxicology and other supportive studies. Pivotal *in vivo* safety studies were conducted in the rat for up to 26 weeks duration and in *Cynomolgus* monkeys for up to 4 weeks duration. Genotoxicity and carcinogenicity studies were not considered relevant given the nature of the molecule and were not performed. As haemophilia B occur almost exclusively in men and very rarely in women, developmental and reproductive toxicity studies were not performed. Local tolerance was assessed as part of the repeat dose toxicity studies in the rat and *Cynomolgus* monkey and in a dedicated local tolerance study in rabbits. The route of administration in the non-clinical studies was intravenous as this is the intended clinical route of administration. All pivotal safety studies were conducted according to Good Laboratory Practice (GLP).

Since the marketing authorisation application (MAA) additional nonclinical studies have been completed in relation to questions around PEG and included in response documents or reported in the Product Safety Update Report (PSUR). To support the current extension of the indication in patients below 12 years of age, two juvenile toxicity studies have been conducted, a preliminary feasibility and tolerability study, and a main juvenile neurotoxicity study, both in male Sprague Dawley rats. Below is a list of the activities completed after the MAA (Table 1).

Table 1. Overview of nonclinical studies completed with nonacog beta pegol after MAA

Discipline	Title	Study ID	Date of finalisation
Pharmacology	-	-	-
Pharmacokinetics			
<i>Method of analysis PEG</i>	Exploratory analysis of the PEG concentration in plasma samples from monkeys using ¹ H-NMR	300017	01-Feb-2017
	Determination of Free 40 kDa PEG in CSF from Rats Dosed with N9-GP by an HPLC-MS/MS Method	307669	21-June-2018
<i>Distribution</i>	Re-assessment of Tissue Distribution of Radioactivity in selected tissue of the Rat by Quantitative Whole Body Autoradiograph	216366	21-Dec-2016
<i>Metabolism</i>	Metabolite profiling of selected plasma, urine and faeces samples from rats, as determined by HPLC fractionation and analysed by accelerated mass spectrometry	215181	24-Sep 2018
<i>Pharmacokinetics-other</i>	Pharmacokinetic evaluation, modelling and simulation in animals and humans based on rat tissue distribution data of N9-GP	300030	07-Sep 2021 (version 2.0)
	Pharmacokinetic modelling and simulation in animals and humans based on rat exposure data following dosing of nonacog beta pegol	322180	22-Sep-2021
Toxicology			
<i>Juvenile toxicity</i>	Preliminary Neonatal Toxicity Study in the Male CD Rat by Subcutaneous and Intravenous Administration	319293	03-Sep 2020
	Immunohistochemistry for PEG and Histopathology on Brains from a Preliminary Juvenile Toxicity Study in the Male CD Rat	321383	19-May 2020
	A Juvenile Neurotoxicity Study in the Male CD Rat by Intravenous Administration, with a 13-Week Recovery Period	319286	10-Sep-2021
	Analysis of Transthyretin and Albumin levels in CSF from the study "NNC0156-0009: A Juvenile Neurotoxicity Study in the Male CD Rat by Intravenous Administration, with a 13-Week Recovery Period"	322216	17-Sep 2021
	Statistical Analysis of TTR and Albumin in CSF from the study "NNC0156-0009: A Juvenile Neurotoxicity Study in the Male CD Rat by Intravenous Administration, with a 13-Week Recovery Period"	322215	21-Sep 2021

2.2.2. Pharmacology

No new primary, secondary or safety pharmacology studies have been conducted since the MAA.

2.2.3. Pharmacokinetics

2.2.3.1. Methods

An exploratory Nuclear Magnetic Resonance (NMR) method was developed during review of the MAA to measure PEG in plasma from rats, monkeys and humans. The NMR method measures both free and conjugated PEG. PEG was measured retrospectively in plasma samples from two anti-drug-antibody (ADA) negative monkeys from the 13-week immunogenicity study, whereas no plasma was available from the 26-week toxicity study in rats. Since the MAA, PEG in plasma from children, adolescent and

adults have been measured and the data reported in PSUR and has been published (Sternebring O, et al., 2019). The NMR assay has also been qualified for use in rat plasma for the neurotoxicity study in juvenile rats.

A significant effort was made to establish a method for detection of PEG in the choroid plexus in the neurotoxicity study in juvenile rats. A HPLC-MS/MS method was pursued and qualified for analysis of low PEG amounts in the small choroid plexus tissue samples.

Table 2. Overview of the different bioanalysis methods for measuring the PEG concentrations

Method of analysis	Study ID	Study type	Species	Matrix	Measures	LLOQ ²
¹ H-NMR	319293	Preliminary tolerability and feasibility study	Rat	Plasma	Total PEG ¹	3 µg/mL (75 nmol/L)
¹ H-NMR	319286	Juvenile neurotoxicity study	Rat	Plasma	Total PEG ¹	3 µg/mL (75 nmol/L)
¹ H-NMR	300017	Feasibility testing of ¹ H-NMR assay	Monkey	Plasma	Total PEG ¹	1.17 µg/mL (29 nmol/L)
HPLC-MS/MS	307669	Bioanalysis report assessing CSF 26-week chronic tox recovery rats	Rat	CSF	Free PEG	50 ng/mL (1.3 nmol/L)
HPLC-MS/MS	319293	Preliminary tolerability and feasibility study	Rat	CSF	Free PEG	50 ng/mL (1.3 nmol/L)
HPLC-MS/MS	319286	Juvenile neurotoxicity study	Rat	CSF	Free PEG	50 ng/mL (1.3 nmol/L)
HPLC-MS/MS	319286	Juvenile neurotoxicity study	Rat	Choroid plexus	Total PEG ¹	25 ng/mL (0.63 nmol/L)
QWBA	216366	Re-assessment of tissue concentrations	Rat	Choroid plexus	Total PEG ¹	10 ng/mL (252 nmol/mL)

¹Total PEG means the sum of conjugated and free 40 kDa PEG. (For NMR, conjugated PEG and free PEG cannot be distinguished by the used method; For HPLC-MS/MS any protein parts in conjugated PEGs will be degraded prior to analysis during the sample preparation procedure). ²The LLOQ are recalculated to nmol/mL or ng/mL using a molecular weight for PEG of 40.000 g/mol and anticipating that 1 g tissue equals 1 mL (for QWBA).

Abbreviations: QWBA = quantitative whole-body autoradiography.

2.2.3.2. Absorption

No new absorption studies have been conducted since MAA. PEG pharmacokinetics (PK) was assessed in the juvenile toxicity studies.

2.2.3.3. Distribution

No new distribution studies were performed since MAA.

In study 216366, the concentrations of radioactivity in liver, kidney and choroid plexus were re-assessed from four rat distribution studies with four PEGylated products [3H]-N9-GP, [3H]-N8-GP, [3H]-N7-GP or [3H]-PEG using an extended number of tissues sections compared to the original assessment (up to four versus one). For the kidney and liver, measurements from the reassessed dataset were very similar to the original dataset giving confidence in the reproducibility of the assessments. For the choroid plexus, the re-assessed data was generally like the original data (<2-fold different), however for some time points the data differed more substantially. Overall, the reassessment gave a more robust data set for choroid plexus regarding variability in concentrations between sampling times compared to the originally produced data set. The data was used to estimate elimination half-lives, which was included in plasma-tissue modelling.

2.2.3.4. Metabolism

At the time of MAA, HPLC fractionation and analysis by accelerated mass spectrometry of urine and faeces from the rat excretion study was still pending. The results supported the conclusion in the MAA from mice and rat, that the protein part of nonacog beta pegol is degraded over time leaving 40 kDa PEG in circulation. The 40 kDa PEG and smaller size PEGs were found to be excreted in urine and faeces.

2.2.3.5. Excretion

No new excretion studies have been performed since MAA.

2.2.3.6. Drug-drug interactions

No new drug-drug interaction studies have been performed since MAA.

2.2.3.7. Other pharmacokinetics

This extension of the MAA includes two new nonclinical juvenile studies: a preliminary feasibility and tolerability study and a main neurotoxicity study, both in juvenile male Sprague Dawley rats. The studies were conducted as an addition to the nonclinical programme to support treatment in patients < 12 years of age.

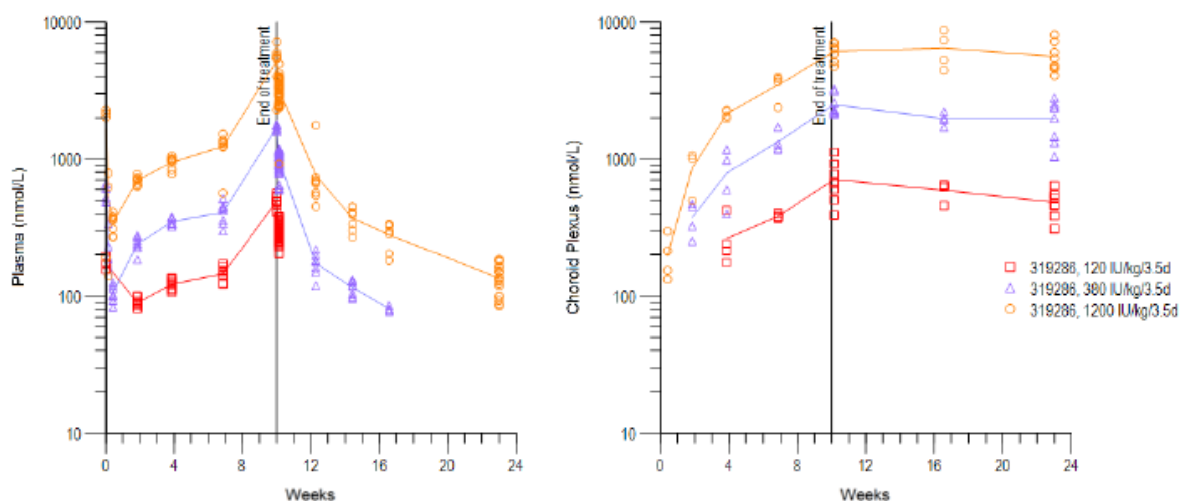
In the preliminary tolerance and feasibility study, pharmacokinetics of PEG was characterised in plasma and cerebrospinal fluid (CSF) following twice weekly i.v. administration of 120-1200 IU/kg nonacog beta pegol to male juvenile rats for approximately 8 weeks (from Day 24 to Day 67 of age). All groups receiving nonacog beta pegol were systemically exposed to PEG on the days of blood sampling, and the plasma PEG concentration increased over time and with increasing dose. The concentration in CSF was evaluated at termination and was below lower limit of quantification (LLOQ) in all samples.

In the main neurotoxicity study in juvenile rats, pharmacokinetics of PEG was characterised in plasma, choroid plexus and CSF following twice weekly i.v. administration of 120- 1200 IU/kg nonacog beta pegol to male juvenile rats for 10 weeks (from Day 21 to Day 91 of age) followed by a 13-week recovery period. All animals administered nonacog beta pegol were systemically exposed to PEG, with plasma AUC increasing in a dose-dependent manner (Figure 1). The exposure was in accordance with the preliminary tolerance and feasibility study and increased with consecutive doses, and exposure declined during the recovery period for all dose levels. Estimated plasma half-life was 42 days.

Choroid plexus tissue dissection was performed at the termination of animals. The tissue samples were analysed for total PEG concentration. Mean choroid plexus PEG exposure increased with increasing doses and with consecutive doses. Exposure declined during the recovery period for all dose levels but remained detectable (Figure 1). Data did not allow for determination of the half-life as the recovery period was too short.

CSF was sampled at the end of the dosing period and during recovery. As for the preliminary study, PEG concentrations were found to be below LLOQ in all samples.

Evaluation of anti-drug antibodies revealed that the antibody frequency in nonacog beta pegol (N9-GP) dosed animals was 1.9% for anti-N9-GP antibodies and 23.6% for anti-PEG antibodies, including the control.



Note: 100 nmol/L corresponds to 4 ug/mL. All plasma samples from Study ID 319286 were not drawn at the same interval following dosing. High exposure was found just after first treatment and just after end of treatment since those samples were taken close to C_{max} (1 and 24 hours post dose) while other samples taken during treatment were taken close to C_{trough} (three days after dosing).

Figure 1. Individual (symbols) and mean (lines) exposure of PEG in plasma (left) and choroid plexus (right) following iv dosing of 120, 380 or 1200 IU/kg twice weekly nonacog beta pegol in the juvenile neurotoxicity study (Study ID 319286)

2.2.3.7.1. PEG PK in plasma and tissue, and prediction PEG concentrations

To support prediction of PEG exposure in plasma and tissues in animals and humans after repeated dosing of nonacog beta pegol, a plasma-tissue model was built initially based on the single dose rat distribution data and updated with repeat dose data from actual plasma and choroid plexus PEG exposure from the rat juvenile toxicity study. A schematic overview of the model is depicted in Figure 2.

Plasma is the central compartment from where PEG is distributed to and from tissues. In tissues, the rate of input is determined by the plasma concentration (dose and dose frequency), and the rate of output is determined by the tissue elimination rate (as determined e.g. in the distribution studies). Steady state in tissues is reached when there is equilibrium between the input and the output rates.

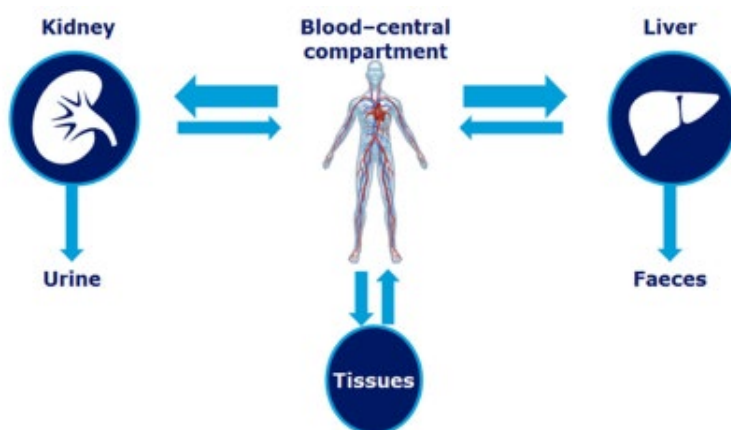


Figure 2. Tissue steady state is reached when there is equilibrium between rate of input from plasma and rate of output, i.e., elimination from the tissue

The plasma-tissue model was used to predict PEG exposure ranges following repeated dosing and to simulate human steady state plasma and tissue PEG concentrations with a once-weekly 40 IU/kg nonacog beta pegol dose and to assess the animal to human exposure ratios (Table 3) and estimated time to reach steady state choroid plexus PEG exposures in human. Acknowledging the limitations of using modelling data, plasma, and choroid plexus exposures as measured at early time points in the juvenile toxicity study where no neurotoxicity has been identified, are covering the observed plasma exposures in human and is in the same range as the predicted human choroid plexus exposures following once-weekly 40 IU/kg nonacog beta pegol treatment to a 40 kg subject. The actual measured plasma PEG concentrations in children, adolescent and adults provide reassurance that PEG steady state concentrations will be reached at levels well below the PEG concentration where no toxicities were observed in the juvenile neurotoxicity study and in 26-week chronic toxicity study in rat. The model predicted PEG to have reached steady state in choroid plexus in humans within approximately 4.5 years.

Table 3. PEG exposure ratio rat/human

	NOAEL dose	Matrix	Concentration in rat (nmol/L)	Concentration in human (nmol/L)	Exposure ratio ^f
Rat juvenile neurotoxicity	1200 IU/kg twice weekly	Plasma	1240 ^a	133-141 ^d	9
		Choroid Plexus	6090 ^b	1310 ^e	5
Rat 26-week repeat-dose toxicity	1200 IU/kg every 5 th day	Plasma	940 ^c	133-141 ^d	7
		Choroid Plexus	8140 ^c	1310 ^e	6

Note: 100 nmol/L corresponds to 4 µg/mL. Study 319286 (M 4.2.3.5.4) (rat juvenile neurotoxicity), Study 212513 (M 4.2.3.2) (rat 26-week toxicity) and Study 322180 (M 4.2.2.7) (modelling report). ^aMean exposures following 7 weeks of treatment (10 weeks sample is not a pre-dose sample). ^bMean exposures following 10 weeks of treatment. ^cSimulated exposure following 26-weeks of dosing using the updated rat plasma-tissue model. ^dMean exposure at steady state in the children ≤ 12 years was 141 nmol/L (5.6 µg/mL) and 133 nmol/L (5.3 µg/mL) in adolescent/adult following weekly prophylactic dose of 40 IU/kg [4]. ^eEstimated steady state level following weekly prophylactic dose of 40 IU/kg to a 40 kg subject (mean body weight in NN7999-3774 trial) using the updated human plasma tissue model. ^fExposure ratio is calculated as rat concentration divided by human concentration.

2.2.4. Toxicology

2.2.4.1. Introduction

Generally, nonacog beta pegol was well tolerated after single doses up to 2000 IU/kg in Wistar rats and after repeat doses up to 1200 IU/kg every fifth day for 26 weeks in Rowett nude rats and 1300 IU/kg/week for 4 weeks in *Cynomolgus* monkey. These dose levels were identified as No-Observed-Adverse effect levels (NOAEL).

In *Cynomolgus* monkeys, mild and transient body tremors were observed at the high dose (3750 IU/kg/week). An explanation for the tremors was not found, but as tremors were transient and only seen at single or two dosing occasions and at a dose level 90-fold the recommended prophylactic clinical dose of 40 IU/kg, they were not considered a safety concern for the clinical dose regimen.

Consistent with the species-foreign nature of human FIX in *Cynomolgus* monkeys, a dose dependent increase in neutralising anti-drug antibodies that cross reacted with endogenous FIX was observed in the mid- (1300 IU/kg/week) and high (3750 IU/kg/week) dose group in the pivotal 4 week repeat dose toxicity study resulting in acquired haemophilia in a number of animals. In a subsequent

immunogenicity study of 13 weeks duration conducted with a lower dose level (200 IU/kg/week), neutralizing anti-drug antibodies cross reacting to endogenous FIX were also found in the majority of the animals. This resulted in acquired haemophilia and reduced exposure after 5-6 doses which precluded meaningful long term toxicity evaluation in this species. Therefore, the Rowett nude rat was introduced to circumvent the immune system in order to be able to assess chronic toxicity of nonacog beta pegol. The Rowett nude rat lacks the thymus and does not develop anti-drug-antibodies.

In both the Rowett nude rat and *Cynomolgus* monkey, a dose related prolongation of PT was seen. Complete reversal to baseline values was evident in samples collected during the treatment free period. *In vitro* experiments confirmed that high concentrations of FIX affect PT times, and the PT time increase, seen in the Rowett nude rats and *Cynomolgus* monkeys, was considered an assay artefact caused by the extremely high FIX plasma concentrations reached. The PT time is not likely to be affected at physiological concentrations of FIX.

In addition to the standard histopathological examination, brain tissue was examined by immunohistochemical (IHC) staining for presence of the PEG part of nonacog beta pegol (Rowett nude rats and monkey) and by transmission electron microscopy (Rowett nude rat). PEG was shown by IHC to be bio-distributed to blood in the blood vessels of the brain, in connective tissue and cytoplasm of epithelial cells of the choroid plexus of the brain in both rat and *Cynomolgus* monkey. No other brain structures showed presence of PEG. PEG presence after nonacog beta pegol treatment was not associated with microscopic signs of cellular vacuolation or dysfunction. However, in nonclinical studies with PEG alone cellular vacuolation due to accumulation of 40 kDa PEG in certain tissues (choroid plexus of brain, macrophages in the interstitium of the choroid plexus, red pulp of the spleen and mandibular and mesenteric lymph nodes) in monkeys and rats observed at doses 200-500 fold higher (rats) or 200 fold higher (*Cynomolgus* monkey) than the PEG load resulting from the recommended clinical dose. Lysosomes with PEG micro-vesicles were observed, in the epithelial cells of the choroid plexus in high dose animals from the 26-week Rowett nude rat study when assessed by transmission electron microscopy. There were no signs of adverse cytological effects in choroid plexus epithelial cells (i.e., the structures of microvilli, tight junctions, mitochondria, rough endoplasmic reticulum, and the Golgi complex were normal). Therefore, the distribution of PEG in lysosomes in the choroid plexus was not considered adverse.

Local tolerance was assessed as part of the repeat dose toxicity study in Rowett nude rats and monkeys and in a dedicated rabbit local tolerance study. Local reactions were primarily related to the injection procedure. Slightly more pronounced local reactions with nonacog beta pegol compared to vehicle control were seen in rabbits after intra-arterial administration but not after intravenous administration in Rowett nude rats or monkey.

A study comparing immunogenicity of nonacog beta pegol and the commercially available rFIX (BeneFIX) at similar repeated exposure levels was performed in rats, with doses of 25 or 200 IU/kg of nonacog beta pegol (weekly) or BeneFIX (daily), respectively. No difference in immunogenicity was seen in rats administered either weekly doses of nonacog beta pegol or daily doses BeneFIX for up to 8 weeks.

2.2.4.2. Selection of species

For the juvenile toxicity studies, the feasibility of using Sprague Dawley rats oppose to the Rowett nude rats was assessed and it was concluded that the Sprague Dawley rat was feasible to use for the juvenile toxicity studies without major impact of anti-PEG antibodies.

2.2.4.3. General toxicity studies

No new general toxicity studies have been performed.

After the MAA, CSF samples collected in the 26-weeks repeat dose toxicity in Rowett nude rats from control and high dose rats after 26 weeks recovery, were analysed retrospectively. PEG was not detectable in CSF from treated animals.

2.2.4.4. Reproductive toxicity

No new reproductive toxicity studies have been performed.

Because of the apparent delay in pubertal onset in the high dose males in the Preliminary Neonatal Toxicity study, the male reproductive organs were weighed in nonacog beta pegol dosed animals. Reproductive organs of control animals were not weighed, as these had already been terminated due to the staggered start of dosing. In the absence of control data, the statistical comparisons incorporating reproductive organ weights were made between nonacog beta pegol treated dose-groups and no changes of toxicological significance were identified. No treatment-related macroscopic abnormalities were observed at scheduled termination (Day 68 of age).

2.2.4.5. Juvenile toxicity

Since the MAA, two juvenile toxicity studies in male Sprague Dawley rats have been conducted, a preliminary feasibility and tolerability study (319293) and a main juvenile neurotoxicity study (319286).

The preliminary feasibility and tolerability study in juvenile male Sprague Dawley rats, concluded that s.c. administration of nonacog beta pegol in juvenile rats pre-weaning was not tolerated, but i.v. administration of nonacog beta pegol post-weaning from Day 24 of age was feasible and tolerable up to 1200 IU/kg/BIW. Plasma PEG exposure increased with dose and was not affected by anti-PEG antibodies. The low dose of 120 IU/kg/BIW was chosen to be similar to clinical steady state plasma exposure of the 40 IU/kg/week prophylaxis dose, the high dose to be 10-fold the clinical plasma exposure at prophylaxis and the mid-dose is the geometric mean between low and high dose, to improve dose-response relationship assessments.

The main juvenile neurotoxicity study in male Sprague Dawley rats concluded that i.v. doses nonacog beta pegol of 120, 380 and 1200 IU/kg/BIW (80 animals/dose group) did not cause any treatment related effects in clinical signs, mortality, growth (body weight and ulna length), food consumption, sexual maturation, fertility, neurobehavior, neurocognitive assessment, morphometric measurements, or neuropathology.

Plasma and choroid plexus PEG exposure increased with dose and dose duration (10 weeks), decreased but remained detectable in plasma in the high dose group and in all dose groups in choroid plexus after a 13-week recovery period. In the choroid plexus exposure had declined 32%, 20% and 8% at end of recovery in the low, mid and high dose group, respectively. PEG was not detectable above LLOQ (50 ng/mL) in CSF.

PEG was detected by IHC staining present in the extravascular space and in epithelial cells within the choroid plexus, in five circumventricular organs (CVOs: the pineal gland, median eminence, subfornical organ, vascular organ of lamina terminalis and area postrema), and motor neurons located in the brainstem (hypoglossal, ambiguous, oculomotorius, accessory abducens, trigeminus and facial motor nuclei). A diffuse stain for PEG was also observed in the nucleus tractus solitarius (NTS). The immunohistochemical stains in the CVOs and cranial motor neurons increased dose dependently in the

treatment period and there was a numerical reduction of PEG stain in all the six organs or brain structures that were analysed (choroid plexus, area postrema, pineal gland, hypoglossal and facial motor nuclei, and the pituitary-pars distalis) in the recovery period. No functional effects related to the PEG staining in the described areas have been observed.

No histopathological changes of the brain were seen. PEG was detected by IHC staining present in the extravascular space and in epithelial cells within the choroid plexus, in three CVOs, and motor neurons in a dose-dependent manner.

Central nervous system (CNS) assessment was evaluated by detailed clinical observations, a functional observational battery (FOB), automated motor activity monitoring, auditory startle response with pre-pulse inhibition and Morris water maze during the dosing and the recovery period and in an extended neuropathology investigation conducted at the end of the dosing and recovery period. Organ weights and gross pathology was assessed at all timepoints and histopathology on reproductive organs, adrenals, and the thyroid gland at end of dosing and recovery.

Non-adverse test item-related histopathological changes commonly observed in relation to the administration of pegylated compounds were observed in the pituitary gland (vacuolated macrophages in Rathke's cleft). There were no associated degenerative or inflammatory changes in the parenchyma of the pituitary gland, and the evaluation of additional special stains did not show any evidence of an effect of treatment in this organ.

CSF samples from the study were analysed non-GLP for Transthyretin (TTR) and albumin as indicators of protein synthesis and transport in the choroid plexus. There was no effect of treatment on CSF albumin or the CSF/plasma albumin ratio. The differences in TTR from controls observed were minor and, in the absence of other findings, considered to be without functional consequences on CNS development and function.

Evaluation of anti-drug antibodies revealed that the antibody frequency in nonacog beta pegol dosed animals was 1.9% for anti-nonacog beta pegol antibodies and 23.6% for anti-PEG antibodies, including the control group.

The highest dose level investigated in this study, 1200 IU/kg/twice weekly nonacog beta pegol was considered the NOAEL.

2.2.5. Ecotoxicity/environmental risk assessment

Nonacog beta pegol is a biological product consisting of a protein (rFIX), coupled to 40 kDa PEG via a chemical linker (cytidin-5'-sialic acid-glycyl). The active pharmaceutical ingredient and the chemical linker are due to their composition expected to be readily biodegradable. 40 kDa PEG is not expected to be readily biodegradable, but it is labelled as non-hazardous according to EU legislation and it has no known adverse effects on humans or the environment. The use of nonacog beta pegol for haemophilia treatment is unlikely to result in any risk to the environment.

2.2.6. Discussion on non-clinical aspects

The SmPC section 5.3 was updated in accordance with the new data in juvenile animals in support of the extension of indication to all age groups.

In the initial MAA, data were submitted for repeat dose toxicity studies in rats and monkeys where 40 kDa PEG deposition was observed by IHC staining in the choroid plexus. Due to the lack of data in juvenile animals and the fact that the potential clinical implications of these animal findings, especially

on neurological and neurobehavioural development were unknown, approval was only granted for patients above 12 years of age.

At the time of the initial MAA, no treatment related vacuolation has been seen in the non-clinical studies with nonacog beta pegol. However, in nonclinical studies with PEG alone, cellular vacuolation due to accumulation of 40 kDa PEG in certain tissues (choroid plexus of brain, macrophages in the interstitium of the choroid plexus, red pulp of the spleen and mandibular and mesenteric lymph nodes) in monkeys and rats observed at doses 200-500 fold higher (rats) or 200 fold higher (*Cynomolgus* monkey) than the PEG load resulting from the recommended clinical dose. Although no neurological symptoms (e.g., tremor) occurred in the clinical studies, accumulation of PEG with possible long-term consequences was regarded to pose a conceivable risk.

The "guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications" (EMA/CHMP/SWP/169215/2005) outlines potential safety concerns that cannot be adequately assessed in the adult population, in standard non-clinical studies, or in clinical trials.

Assessment of neurotoxicity studies are required if the chemical/pharmacological class of compounds or previous studies in humans or animals gives cause for concern for the developing nervous system or influences for neuroendocrine system balance.

Possible neurotoxicity of PEG or pegylated compounds was analysed in literature (Briani *et al.*, 2006; Hussain *et al.*, 2019).

To further elucidate on this issue and to fill the data gap in juvenile animals and children, the MAH within this application for extension of indication provided new data with nonacog beta pegol in juvenile rats together with clinical data for the targeted population. No new data on PEG alone was submitted.

A preliminary tolerability and feasibility study and a neurotoxicity study, both in juvenile male rats, were conducted to investigate PEG kinetics and the potential impact of PEG on CNS development, function, and neuropathology, to support the extension of indication to patients below 12 years of age. Male rats were used as haemophilia almost exclusively occurs in the male human population. All studies used the intravenous (IV) route of administration, which is also the proposed clinical route of administration.

With regards to the choice of the animal model, the MAH reported the following:

"Consistent with the species-foreign nature of human FIX in Cynomolgus monkeys, a dose dependent increase in neutralising anti-drug antibodies that cross reacted with endogenous FIX was observed in the pivotal 4 week repeat dose toxicity study resulting in acquired haemophilia in a number of animals. Therefore, the Rowett nude rat was introduced to circumvent the immune system in order to be able to assess chronic toxicity of nonacog beta pegol. The Rowett nude rat lacks the thymus and does not develop anti-drug-antibodies. In both the Rowett nude rat and Cynomolgus monkey, a dose related prolongation of PT was seen."

"For the juvenile toxicity studies, the feasibility of using Sprague Dawley rats oppose to the Rowett nude rats (The Rowett nude rat lacks the thymus and does not develop anti-drug-antibodies) was assessed and it was concluded that the Sprague Dawley rat was feasible to use for the juvenile toxicity studies without major impact of anti-PEG antibodies".

This is in accordance with the effective guideline stating that "juvenile animal species should be appropriate for evaluating toxicity in endpoints relevant for the intended paediatric population. With respect to repeat dose toxicity studies, rats and dogs are traditionally the species of first choice."

The need to have a reference system with historical control data, in order to correctly judge the possible toxic effects of the treatment was taken into account in the choice of the SD rats.

Overall, the MAH's justification for the selection of species is acceptable.

The selected doses of 120-1200 IU/kg correspond to the 1-10-fold clinical PEG plasma exposure and according to the provided plasma-tissue model are comparable to the predicted clinical choroid plexus PEG exposure.

A juvenile animal neurotoxicity study was conducted to evaluate the potential neurotoxicity of nonacog beta pegol after i.v. administration of 120-1200 IU/kg/twice weekly to juvenile male rats from D21 to D91, followed by a 13-week recovery period. As expected from previous data, also with other pegylated compounds, PEG was determined in the choroid plexus, in five circumventricular organs, specifically the area postrema, pineal gland, median eminence, subfornical organ, and the vascular organ of lamina terminalis, as well as in the nucleus tractus solitarius. PEG was also detected in the cytoplasm of cranial motor neurons located in the brainstem, specifically the hypoglossal, ambiguous, oculomotorius, accessory abducens, trigeminus and facial motor nuclei.

However, alterations on neurobehavioral and neurocognitive development or other neuropathological changes were not observed in this conducted repeat-dose juvenile rat toxicity study in any of the treated animals. CNS assessment was evaluated by detailed clinical observations, a functional observational battery (FOB), automated motor activity monitoring, auditory startle response with pre-pulse inhibition and Morris water maze during the dosing and the recovery period and in an extended neuropathology investigation conducted at the end of the dosing and recovery period.

In addition to neurological endpoints, the juvenile rats were also examined for their general condition, sexual maturation, and growth without any adverse findings reported. Although dedicated studies on reproductive toxicity were not performed in animals for nonacog beta pegol, within the juvenile rat study, fertility and reproductive organs of male rats was regarded unaffected following 9 weeks of treatment.

I.v. administration of 120, 600 or 1200 IU/kg/twice weekly from Day 24 of age was well tolerated, with effects limited to minor, transient bruising at the injection site in all groups (including controls), an increase in testes weights and an apparent 4-day delay in attainment of sexual maturation in males given 1200 IU/kg/twice weekly, which may be related to treatment. Such as recommended, the highest dose achieved some identifiable effects, however these effects were considered as non-adverse. The highest dose level investigated in this study, 1200 IU/kg/twice weekly nonacog beta pegol was considered the NOAEL.

PEG exposure in treated animals was shown to increase in a dose- and treatment time-dependent manner. PEG was below LLOQ in the CSF and IHC stainings confirmed that PEG was not passing the blood-brain barrier in nonacog beta pegol treated animals.

PEG was still detectable in all animals after the 13-week recovery period, however image analyses revealed a slight reduction of PEG staining during recovery in all tissues analysed, including choroid plexus. In previously conducted distribution and excretion studies in mice and rats, the 40 kDa PEG moiety was confirmed to be distributed to various tissues and organs tested and elimination from organs was shown to occur mainly via plasma in urine and faeces.

The data submitted in juvenile animals treated with nonacog beta pegol revealed only slight accumulation in macrophages in the pituitary gland, which was considered to represent a normal physiological processing of foreign material in that cell type. However, at PEG exposure levels showing acceptable safety margins compared to clinical dosing, no other adverse findings were observed that would indicate an increased risk of PEG accumulation in juvenile rats.

According to the updated tissue-plasma model, the actual measured plasma PEG concentrations in children, adolescent and adults provide reassurance that PEG steady state concentrations will be reached at levels well below the PEG concentration where no toxicities were observed in the juvenile neurotoxicity study and in 26-week chronic toxicity study in rat. Steady state in plasma could also be reached by accumulation of PEG in various tissues instead of elimination of the PEG moiety, however based on the original and newly provided data altogether this scenario appears rather theoretical and nonclinical data did not reveal any adverse toxicities that could be related to such accumulation.

CSF samples from the study were analysed for transthyretin and albumin as indicators of protein synthesis and transport in the choroid plexus. No treatment effect on CSF albumin or the CSF/plasma albumin ratio was observed. Reduction in transthyretin levels was observed in control animals at the end of dosing and thus deviations to control were attributed to the high variation observed in control animals over time, which did not show dose-response in any of the dose groups and were thus not regarded treatment-related. In the absence of any other findings in the juvenile toxicity studies, those transthyretin alterations can thus be considered to be without functional consequences on neurological development and function.

Vacuole formation in the choroid plexus of animals after PEG exposure was generally considered an uncertainty with regards to its unknown clinical impact and, among others, was one of the factors to limit the original indication of nonacog beta pegol to patients 12 years of age and above.

The MAH herewith provided new data on vacuolisation in juvenile rats. In the conducted toxicity study accumulation of PEG in the choroid plexus and vacuole formation in various organs was reported. Vacuole formation was observed in the choroid plexus epithelial cells across all treatment groups at doses 6-60-fold the weekly clinical dose of 40 IU/kg (corresponding to 1-10 times the clinical PEG plasma levels and according to the modelling provided are comparable or well above the predicted clinical choroid plexus PEG exposure). However, vacuole formation was also observed in the control animals at the same incidence and severity. Moreover, these vacuoles did not stain positive for PEG in the treatment groups (nor in the control). Vacuole formation in the choroid plexus was only reported in a limited number of (treated) animals and in most of these animals, the vacuole formation was reported as 'minimal or slight' and did not follow dose- or time-dependent manner, thus indicating no pattern. Thus, the MAH considered the vacuolation in choroid plexus epithelial cells in rats to be non-adverse and not related to nonacog beta pegol treatment.

PEG-positively stained vacuolated macrophages were found in Rathke's cleft in the pituitary gland in animals terminated during the treatment period and in animals after 13 weeks of recovery. The accumulation of PEG in vacuoles in macrophages in Rathke's cleft were considered to represent a normal physiological processing of foreign material.

According to data provided by the MAH based on a plasma-tissue model to predict PEG exposure ratios rat/human after once-weekly 40 IU/kg nonacog beta pegol administration to 40 kg subjects, (predicted) PEG exposure ratios ranged from at least 5-fold in the choroid plexus up to 9-fold in plasma compared to the NOAEL of 1200 IU/kg/BW of the juvenile toxicity study, thus resulting in acceptable exposure safety margins for PEG. The same model predicted PEG to have reached steady state in choroid plexus in humans after approximately 4.5 years.

Although such predictions show limitations and should be used with caution, these non-clinical data altogether suggest the risk for adverse effects in children caused by PEG exposure to be minimal. No non-clinical neurological or neurocognitive adverse findings were observed in the juvenile rat study up to the highest tested dose. However, potential clinical implications were further elucidated (please refer to the clinical safety discussion of this assessment report).

2.2.7. Conclusion on the non-clinical aspects

Nonacog beta pegol administration to juvenile male rats revealed no adverse effects up to the highest tested dose of 1200 IU/kg/BIW (60-fold the weekly clinical dose of 40 IU/kg). 1200 IU/kg/BIW was thus considered the NOAEL in this study.

Juvenile male rats (3 to 13 weeks of age corresponding to 2 to 16 years of age in humans) exposed to PEG (from nonacog beta pegol) at acceptable safety margins (up to 10 times the clinical PEG plasma levels and according to plasma-tissue modelling comparable or well above the predicted clinical choroid plexus PEG exposure) did not show any signs of neurotoxic or adverse neurobehavioral development.

In the initial MAA, accumulation of PEG after nonacog beta pegol treatment was only observed at low levels, however increased in studies using 40 kDa PEG alone. With a half-life of 15-18 days of the PEG moiety after nonacog beta pegol treatment, some accumulation by weekly administration of nonacog beta pegol in clinical prophylactic dose regimen was thus regarded possible, with the long-term consequences of these findings, especially in children, unknown at the time of the original MA.

The data submitted in juvenile animals treated with nonacog beta pegol revealed only slight accumulation in macrophages in the pituitary gland, which was considered to represent a normal physiological processing of foreign material in that cell type. However, at PEG exposure levels showing acceptable safety margins compared to clinical dosing, no other adverse findings were observed that would indicate an increased risk of PEG accumulation in juvenile rats. A dedicated animal model to investigate long-term consequences of potential PEG accumulation in (juvenile) animals is still not available, however the provided nonclinical data in juvenile rats focussing on neurologic development appears reassuring and supports the newly provided clinical data in the target population, which obviously constitutes the most important increase in knowledge, compared to the initial MAA.

As already shown in adult rats and monkey in the initial MAA, no PEG related vacuolation was observed in the juvenile rats' choroid plexus.

No new data on PEG alone treatment, which was shown to induce cellular vacuolation due to accumulation of 40 kDa PEG in certain tissues (including choroid plexus of brain, macrophages in the interstitium of the choroid plexus, red pulp of the spleen and mandibular and mesenteric lymph nodes) in adult monkeys and rats in the initial MAA, were submitted. However, these findings were observed at doses 200-500 fold higher than the PEG levels resulting from the recommended clinical dose, without any adverse (neurological) effects observed in these animals. Although the human relevance of PEG alone treatment at such high supraclinical exposure levels is questionable, it was concluded that due to the uncertainties around this issue and missing data in juvenile animals and children, use of nonacog beta pegol in the paediatric population at all ages, was not conceivable at that time.

However, in the course of this application for extension of indication to all ages the MAH submitted repeat dose toxicity data in juvenile animals (without any adverse findings) together with promising clinical data in the targeted population of children below 12 years of age, with data from both disciplines pointing against this theoretical risk of detrimental effects on neuronal development due to potential PEG accumulation and/or vacuolisation. The newly provided nonclinical data in juvenile animals together with the nonclinical data on nonacog beta pegol submitted in the initial MAA thus generally support treatment with nonacog beta pegol in children below 12 years of age from a nonclinical perspective. However, the nonclinical studies provided do not allow a definite conclusion to be drawn on the risk for children aged less than 2 years since the juvenile studies provided do not cover this period (rats treated from 3 to 13 weeks of age corresponding to 2 to 16 years of age in humans). Please refer to further discussion on this issue in the clinical section and the Benefit-Risk Balance.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of nonacog beta pegol.

Considering the above data, nonacog beta pegol is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

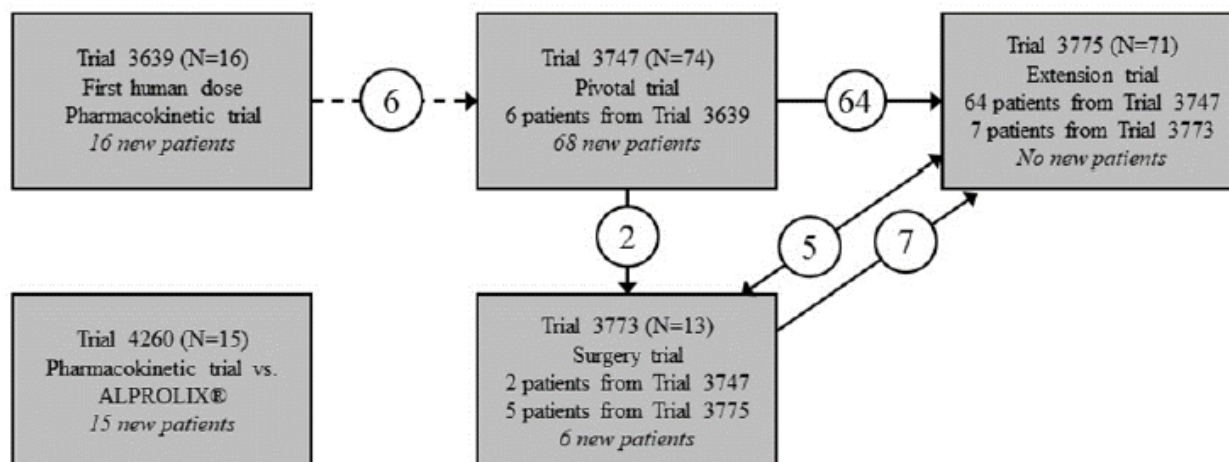
GCP

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

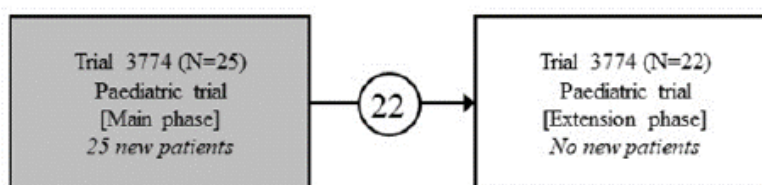
The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Previously treated patients – adults and adolescents



Previously treated patients – children ≤ 12 years



Previously untreated patients – children < 6 years

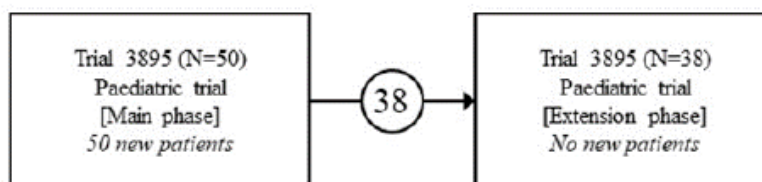
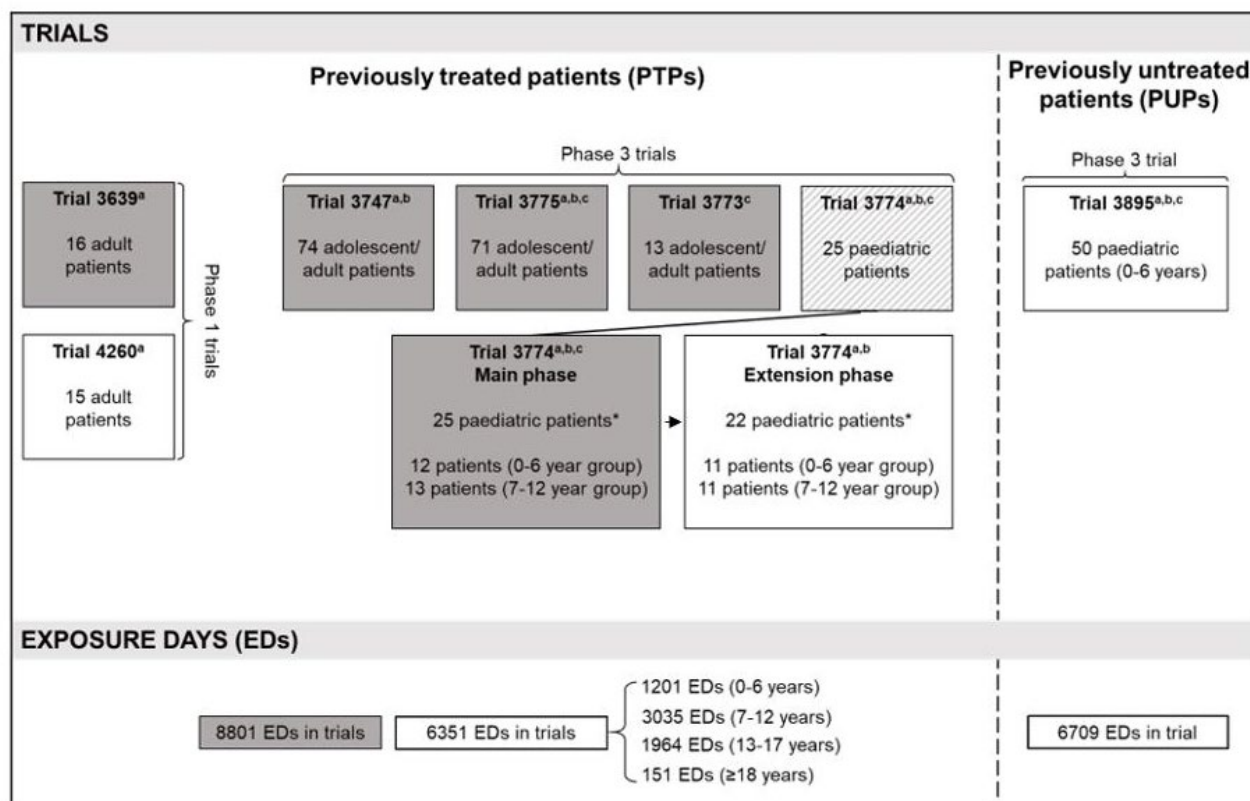
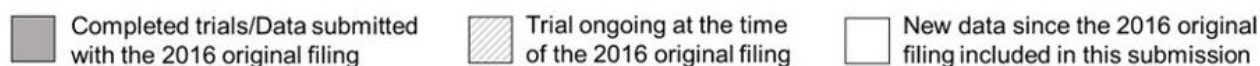


Figure 3: Overview of clinical studies and flow of patients in the clinical development programme for nonacog beta pegol

The flow of patients through the trials is illustrated in Figure 3. In the completed trials (marked in grey), a total of 130 unique PTPs have been exposed to nonacog beta pegol. The number of patients exposed to nonacog beta pegol for the first time in each trial is indicated as number of new patients in italics. Several patients in Trials 3639, 3747, 3773 and 3775 participated in more than one trial which explains that the sum of patients (N) in the individual trials is higher than the total number of unique patients. In trial 3774, 1 patient withdrew during the main phase and 2 patients did not continue to the extension phase. In Trial 3895, 50 unique PUPs have been exposed to nonacog beta pegol; 5 patients withdrew during the main phase, 1 patient did not enter the extension phase and 6 patients are yet to complete the main phase.

In total, 75 children (0-12 years; previously treated patients [PTPs] and untreated paediatric patients [PUPs]), 18 adolescents (13-17 years old; PTPs) and 87 adults (18-65 years old; PTPs) have been exposed to nonacog beta pegol within the development programme. Since the original filing in 2016, two phase 3 trials are ongoing: Trial 3774 in PTPs and Trial 3895 in PUPs; and one phase 1 trial has been completed (Trial 4260).



a: On-demand treatment; b: Prophylaxis treatment; c: Major surgery treatment

* Given the long duration of the trial, paediatric patients became adolescents or adults at some point during the trial. In the 0-6 year age group, 10 patients turned 7-12 years including 2 patients who further turned 13-17 years. In the 7-12 year age group, 10 patients turned 13-17 years including 3 patients who further turned ≥18 years old.

The number of patients exposed to nonacog beta pegol are presented in this figure.

Figure 4: Overview of new clinical trial data since the 2016 original filing

2.3.2. Pharmacokinetics

Trial ID: NN7999-3774

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

Given the long duration of trial 3774 (planned for up to 10 years of patient exposure), the children participating in the trial are expected to have passed several age groups. As a result, at the current data cut-off (25-Nov-2020) there were 3 patients present in the adult age group and 12 patients present in the adolescent age group. It is noted that the FIX trough levels are known to increase with patients' age.

FIX activity

Single-dose PK profiles and PK parameters were assessed at visit 2 and were presented at the initial MAA. For detailed presentation of the results please refer to the EPAR of Refixia.

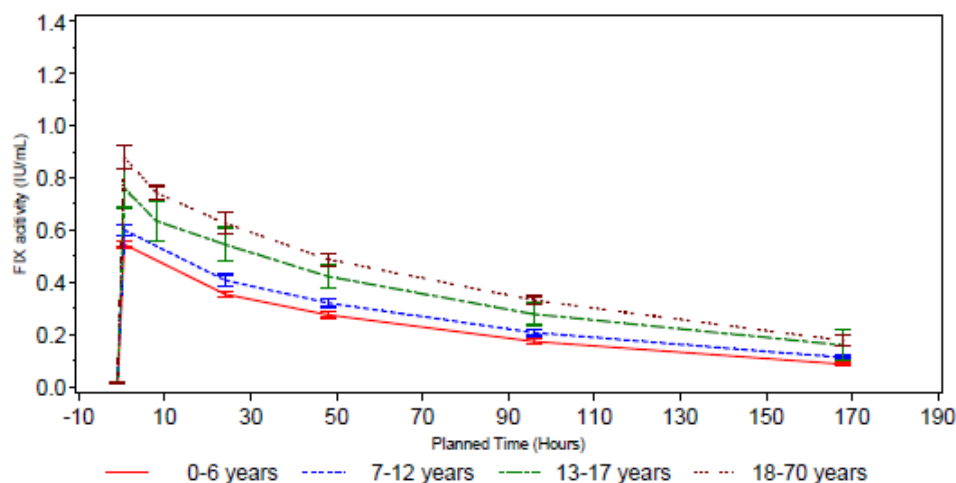
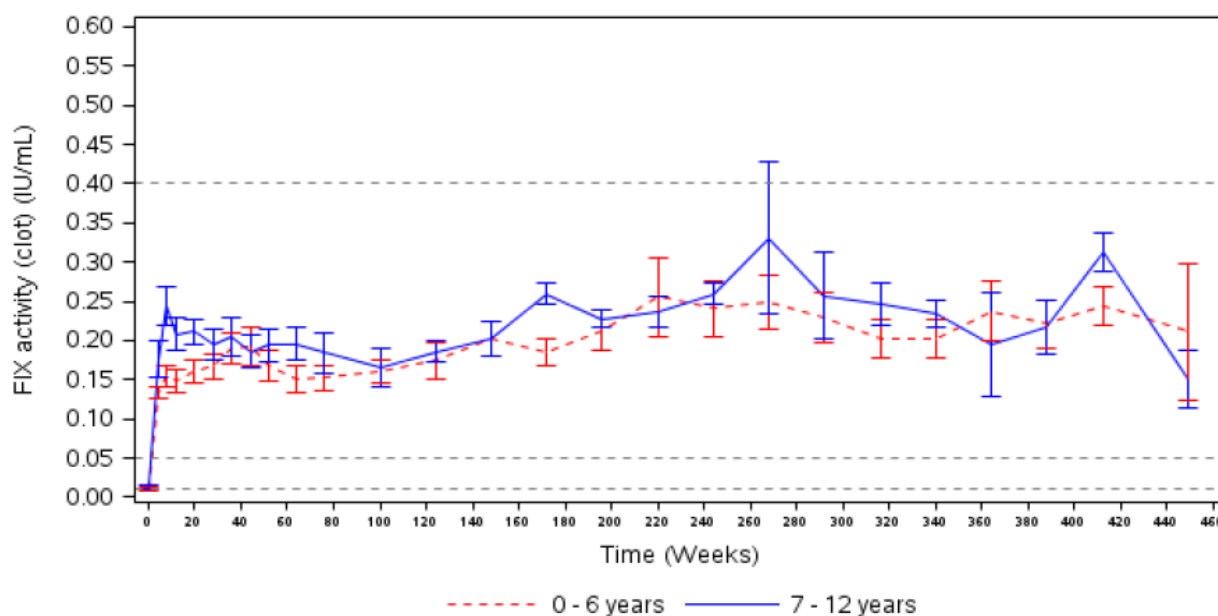


Figure 5: Mean single-dose pharmacokinetic profiles of nonacog beta pegol, derived from Trials 3747 and 3774 (main phase)

For the analysis of **steady-state FIX trough** only pre-dose samples taken at least 5 days and no more than 10 days after last dose, as well as measurements taken at least 14 days after last bleeds, were included. This was to ensure that the FIX activity levels in the samples were representative of the trough FIX activity levels observed between regular prophylaxis treatments. The FIX trough levels at steady state remained constant throughout the trial.



Mean $\pm$ SEM

The horizontal dotted lines represent upper FIX activity levels for definitions of severe (0.01 IU/mL), moderate (0.05 IU/mL) and mild (0.40 IU/mL) haemophilia B.

Only predose measurements taken at least 5 days and no more than 10 days after last dose as well as measurements taken at least 14 days after last bleeding episode are included.

450 week assessment denotes end of trial visit.

Figure 6: Mean pre-dose Factor IX activity (IU/mL; clot assay) – Safety analysis set

The total estimated mean FIX trough level at steady state based on the mixed model analysis was 0.181 IU/mL [0.160; 0.204]95%CI for all patients and was 0.146 [0.127; 0.167]95%CI in the 0-6-year age group, 0.195 [0.172; 0.220]95%CI in the 7-12 year age group and 0.213 [0.185; 0.247]95%CI in the 13-17 year age group. For the 18-70 year age group, there were only 3 trough values included in the analysis therefore model estimates should be interpreted with caution. As expected, FIX trough levels at steady state increased with age.

Table 4: Analysis of Factor IX trough levels, one stage clotting assay by actual age groups – full analysis set – trial 3774 (cut-off date 25th of November 2020)

	Younger children (0-6 years)	Older children (7-12 years)	Adolescents (13-17 years)	Adults (18-70 years)	Total
Number of patients	12	23	12	3	25
Number of trough values included in the analysis ^a	126	228	70	3	427
Number of trough values excluded from the analysis ^a	6	13	25	6	50
Number of values below lower limit of quantification ^b	0	0	0	0	0
Mixed model results ^c					
Mean trough level (IU/mL)	0.146	0.195	0.213	0.114	0.181
95% CI	0.127; 0.167	0.172; 0.220	0.185; 0.247	0.077; 0.169	0.160; 0.204

^a 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.

^b Plasma activities below lower limit of quantification (LLOQ) of 0.01 IU/mL are set to half of LLOQ (0.005 IU/mL).

^c The analysis is based on a mixed model on the log-transformed plasma concentrations with patient as a random effect.

^d The cut-off date for data included from the trial was 25-Nov-2020.

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.

Trial ID: NN7999-3895

FIX activity

Mean steady state FIX trough levels assessed in 47 PUPs aged ≤6 years were within the range for mild haemophilia (between 0.05 and 0.4 IU/mL) and remained constant throughout the trial with an estimated mean of 0.156 IU/mL [0.144; 0.170]95% CI in the prophylaxis treatment period. In the main phase of the trial, the trough value in the PUPs was comparable to that of the trough values observed in the younger PTP children at the same age group. The mean incremental recovery was between 0.012-0.014 (IU/mL)/(IU/kg) for all visits, including both the pre-prophylaxis and prophylaxis treatment periods. In the prophylaxis treatment period, mean (SD) FIX activity 30 minutes post-dose increased slightly from visit 1 (0.563 [0.113] IU/mL) until visit 28 (0.842 [0.180] IU/mL), after which it was not measured. This was not necessarily a trend, due to very small change in FIX activity.

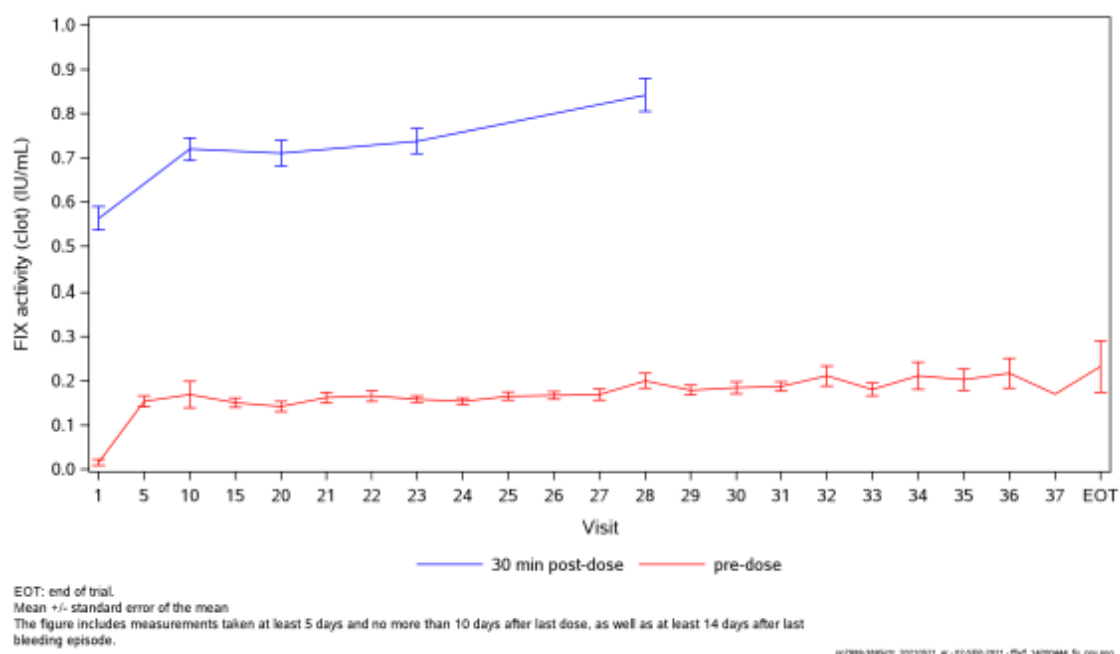


Figure 7: Mean profiles of Factor IX activity (IU/mL; clot assay) for PUPs on prophylaxis – full analysis set

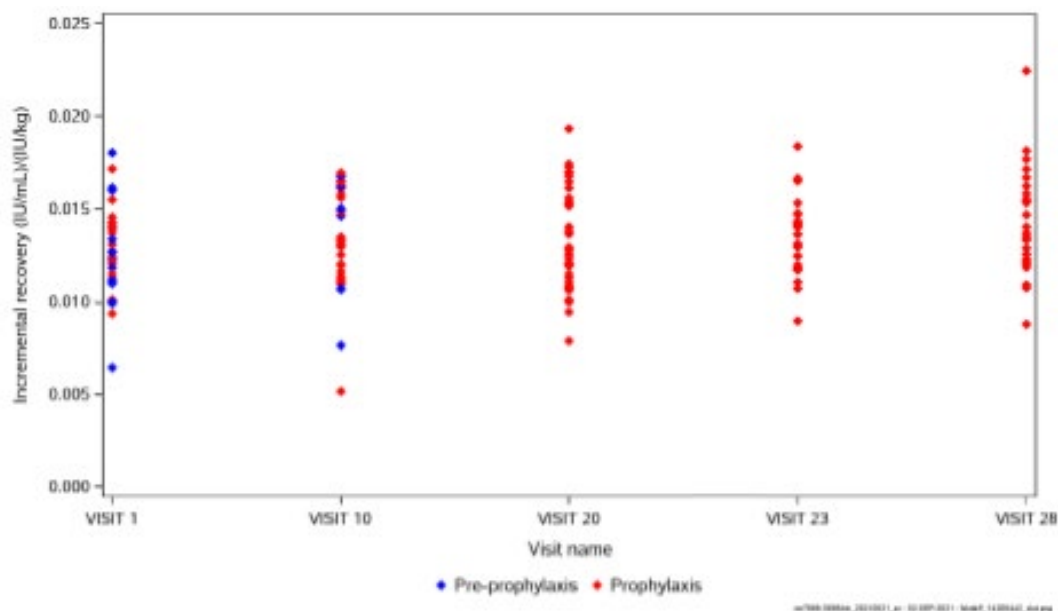


Figure 8: Plot of incremental recovery (IR) at 30 minutes (IU/mL)/(IU/kg) – full analysis set

2.3.3. Pharmacodynamics

The FIX activity used for the pharmacokinetic assessment is known to correlate with clinical efficacy of FIX products. Thus, the FIX activity is to be considered pharmacodynamic in nature, as it reflects the biologic action of nonacog beta pegol. Hence, no other pharmacodynamics endpoints have been assessed.

2.3.4. Discussion on clinical pharmacology

Pharmacokinetic data on Factor IX activity after single exposure in paediatric patients were reported during initial MAA of Refixia and can be found in the respective EPAR. In short, plasma FIX activity levels and incremental recovery appeared to be lower in children compared to adults and adolescents, whereas body weight-adjusted clearance appeared to be higher in children. This observation is principally in line with other authorised Factor IX products. It is to be noted that data from study 3774 in the age group of patients below 2 years are based on data from 3 patients only and conclusions should be made cautiously. However, it is noted that included numbers for PUPs in trial 3895 appear adequate for this age subgroup (n=41 patients <2 years). The actual dose was determined by the volume administered and all pharmacokinetic endpoints for nonacog beta pegol were derived from pharmacokinetic profiles using non-compartmental methods, which is supported.

With the extension data from study 3774 the MAH now provides steady-state Factor IX trough levels measured from pre-dose samples up to 450 weeks after treatment initiation. Throughout the reported period patients of both age groups show mean Factor IX trough levels 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).

Total estimated mean steady state Factor IX trough levels in PUPs (measured at visits pre-dose with the one-stage clotting assay) are comparable to mean levels for PTPs of the same age group (0.156 IU/mL and 0.146 IU/mL for PUPs and PTPs 0-6 years, respectively). Further in line with results for PTPs ≤6 years old, trough levels also remained stable for PUPs throughout the observation period. It is acknowledged that mean incremental recovery (IR; at 30 minutes measured with the one-stage clotting assay) was principally comparable in PUPs (i.e. 0.012-0.014 (IU/mL)/(IU/kg) throughout all visits) to mean levels reported for PTPs during the main phase of study 3774 (i.e. 0.015 (IU/mL)/(IU/kg) for younger children 0-6 years old and 0.016 (IU/mL)/(IU/kg) for older children 7-12 years old). The slightly lower mean IR in PUPs is in line with expected results for younger subjects, as the mean age of PUPs was below the mean age of PTPs in the 0-6 years age group of study 3774 (i.e. 0.3 years in trial 3895 and 3.1 years in trial 3774). Upon request, the MAH provided information on all paediatric subjects (PUPs and PTPs) with IR values <0.012 (IU/mL)/(IU/kg). A total of 25 patients (Trial 3895, PUPs) and 10 patients (Trial 3774, PTPs) had an IR below 0.012 (IU/mL)/(IU/kg) at one or more visits. Only one paediatric subject (PUP) from 35 subjects (PUPs and PTPs) with IR values <0.012 (IU/mL)/(IU/kg) had a positive test for anti-drug antibodies. No major differences in terms of efficacy were observed in patients with an IR <0.012 (IU/mL)/(IU/kg) in the data analysed for PUPs and PTPs. A single subject (PUP) had an IR value below 0.006 (IU/mL)/(IU/kg) at a single visit during prophylaxis treatment (2 years old subject with IR 0.0052 (IU/mL)/(IU/kg) at exposure day 10). However, reported FIX activity 30 minutes post dosing does not give reason of concern (trough value of 0.1280 IU/mL, C30min: 0.355 IU/mL) and the same subject had only one further IR value below 0.012 (IU/mL)/(IU/kg) at exposure day 1 (i.e. 0.01 (IU/mL)/(IU/kg)). Importantly, no bleeding episodes were reported for this subject up to 1 month before the visit with IR value below 0.006 (IU/mL)/(IU/kg) and the subject did not have N9-GP binding antibodies or FIX inhibitors.

2.3.5. Conclusions on clinical pharmacology

Prophylactic dosing of 40 IU/kg once a week appears to provide stable steady state trough levels for a long-term in paediatric previously treated (≤12 years) and previously untreated patients (≤6 years). Thus, the recommended dosing in paediatric patients is supported by PK data on Factor IX activity during prophylactic dosing with nonacog beta pegol.

2.4. Clinical efficacy

The current application seeks extension of indication for treatment and prophylaxis of bleeding episodes in children (<12 years of age) with haemophilia B. The cut-off date for data presented in this application is 25-Nov-2020. New clinical efficacy data from two phase 3 trials (trial 3774 in PTPs and trial 3895 in PUPs) in paediatric patients with haemophilia B in support of a prophylaxis indication in children and adults is provided. Both trials assessed once-weekly prophylaxis with 40 IU/kg nonacog beta pegol in the treatment of paediatric patients with haemophilia B. Trial 3895 also included an optional pre-prophylaxis treatment period (where patients received on-demand treatment of bleeding episodes and/or had a slow start-up of prophylaxis with a dose of 40 IU/kg at intervals longer than a week) prior to initiating prophylaxis treatment at 24 months of age or 20 Exposure Days (EDs), whichever came first. Given the long duration of trial 3774, paediatric patients became adolescents or adults at some point during the trial.

2.4.1. Main studies

Trial ID: NN7999-3774

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

An open-label, single-arm, multinational, non-controlled trial investigating safety, efficacy and pharmacokinetics of NNC-0156-0000-0009 (nonacog beta pegol) in prophylaxis and treatment of breakthrough bleeds 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 $\leq 2\%$ 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 $< 50,000/\mu\text{L}$ 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 $\leq 200/\mu\text{L}$.
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)

Objectives

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 ($t_{1/2}$) (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

No randomisation was performed due to the single-arm nature of both submitted paediatric trials (NN7999-3774 and NN7999-3895).

Blinding (masking)

Blinding does not apply as both submitted paediatric trials (NN7999-3774 and NN7999-3895) were open-label trials

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 and 25 patients were enrolled and exposed to the trial product in the main phase (Figure 9), of which 12 patients were in the 0-6 year age group and 13 patients were in the 7-12 year age group at trial entry. Three (3) of the 28 patients failed screening. One (1) patient withdrew consent during the main phase. Of the 24 patients who completed the main phase, 22 patients (88%) entered the extension phase (11 patients in each age groups) while 2 patients did not continue into the extension phase. The two patients fulfilled withdrawal criteria #5 (i.e. Incapacity or unwillingness to follow trial procedures). Of the 22 patients, 12 patients remained in the trial and 10 patients withdrew during the extension phase as of interim cut-off. The reasons for withdrawal are presented in Table 5. None of the patients withdrew due to AEs. All withdrawn patients contributed with data until the date of withdrawal. The FAS and SAS consisted of 25 patients.

Patient disposition

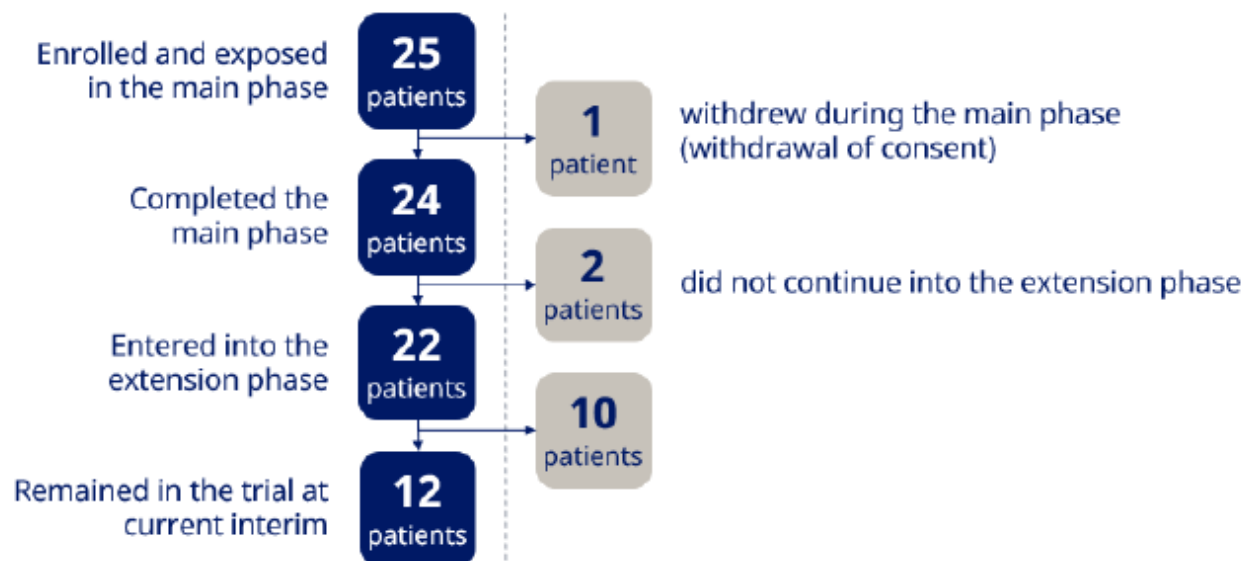


Figure 9: Patient Disposition

Table 5: Withdrawn patients in the extension phase and reasons for withdrawal

Withdrawal criteria/discontinuation term or event
Withdrawal criteria #5 (Incapacity or unwillingness to follow trial procedures)
Non-compliance
Withdrawal of consent
Other (parental concern over PEGylated product)
Other (discontinuation of the principal investigator at site)
Other (study team lost contact with the patient for some months)
Other (patient moved out of province)
Other (trial product not approved for prophylaxis)

A total of 10 patients underwent 17 minor surgeries and 1 patient underwent 1 major surgery.

Given the long duration of the combined main and extension phases with an average treatment period of 6.03 years, 10 of the 12 patients enrolled in the 0-6 year age group grew into 7-12 years including 2 patients who further grew into adolescents (13-17 year age group). Likewise, of the 13 patients enrolled in the 7-12 year age group, 10 patients grew into adolescents including 3 patients who further grew into adults. Thus, the trial included 12 adolescent patients and 3 adult patients.

Recruitment

Table 6: Screening failures

Age at baseline	Country	Race	Ethnicity	Exposed	Specification of other failure reason	Inclusion criteria as failure reason	Exclusion criteria as failure reason
6	United States of America	White	Hispanic or latino	No			E4
12	United States of America	White	Not hispanic or latino	No			E5
11	United States of America			No	Normal clinic procedure requires patients get v/s and weight before any visit; patient's BMI disqualified him 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.

Conduct of the study

Changes in planned analyses

Additional analysis of the estimated mean steady state FIX trough levels were analysed using a mixed model on the log-transformed plasma concentrations with patient as a random effect. The mean trough level was presented back-transformed to the natural scale. Plasma concentrations below LLOQ were set to half the value of the LLOQ. There was a change in the definition of IR from the protocol as the baseline subtracted FIX activity was used for calculation.

Given the rarity of major surgery in this trial, the time period when the patients stopped weekly prophylaxis to go to major surgery and to the date and time when patient resumed weekly prophylaxis treatment and the bleeding episodes happened during this time period (if any) were included in the estimation of the annualised bleeding rate during prophylaxis treatment.

Given the long duration of the combined main and extension phase, some patients became adolescents or even adults at some point during the trial. Further analyses were performed to evaluate the exposure, efficacy and safety of once weekly prophylaxis based on patients' actual age groups at the time of exposure or event, by age groups of 0-6 years, 7-12 years, 13-17 years and 18-70 years. It should be noted that adolescent and adult patients have been exposed to nonacog beta pegol for a longer time compared to younger age groups, hence any comparison between the actual age groups should be interpreted with caution.

In addition to the above analysis, the majority of the analyses were performed based on patients' age at trial entry to ensure consistency in trial reporting. To analyse the trajectories of neurological examinations over time, shift plots were added by examining the proportion of neurological examination items which shifted between every two consecutive examinations. For each item, the shifts were categorised into one the three following groups:

- Shift up (improved): from abnormal to normal findings
- Shift down (worsening): from normal to abnormal findings
- No change: from abnormal to abnormal; or from normal to normal findings

To analyse the trajectories of NCA over time, the following outputs of z-scores (against eTHINK) were added/adjusted in addition to the pre-specified individual plots:

- Summary tables of z-scores/change from prior assessment/change from initial assessment by assessment as well in total, which replaced the pre-specified summary table by visit as the NCA were performed at very different visits leading to sparse data by visit;
- Heat maps of mean value of change in z-scores at each subsequent assessment from initial assessment;
- Random regression model of z-scores, with exposure day as fixed effect and subject as random effect, allowing random intercept and random slope for exposure day for each individual subject. Due to limited amount of neurocognitive data at this interim, the random regression model was only performed for executive function domain and attention/processing speed domain which were collected for all countries.

The initial and subsequent categorical evaluation (clinical concern) from the External Expert Review Panel (EERP) meetings were listed, together with corresponding exposure days (EDs).

For the preparation of EERP summary report, additional statistical outputs (summary tables and listing of Clinical Concern/Contributing Factor; statistical analyses of Clinical Concern by patient demographics/z-scores; statistical analyses of Clinical Concern/Contributing factor by SDH/HH parameters; heat maps of z-scores; summary table and shift plots of neurological examinations) were provided per request by members of EERP.

No other changes to the planned statistical analyses were performed.

Protocol amendments

A total of 10 substantial amendments were made to the protocol at the time of cut-off (25 November 2020) for this interim analysis. All protocol amendments were approved according to local requirements prior to implementation. None of the substantial amendments issued after the first visit were considered to have any influence on the interpretation of the results of the trial.

Three (3) patients entered the extension phase before Amendment 4 was implemented. These patients were however not individually dosed due to the near execution of the amendment and continued on the 40 IU/kg regimen as in the main phase of the trial. Amendment 7 was not submitted to the health authorities (please see Table below for details).

Table 7: Summary of substantial amendments to the study protocol

Amendment number	Issue date	Timing of change (before/after FPFV)	Countries affected	Key changes
1	30-March-2012	Before	Global	• Changes in the description of the visual appearance of the investigational medicinal product. • Information on stop time of bleeds.
2	10-July-2012	After	Turkey	• Change in inclusion and exclusion criteria related to age of Turkish trial patients. Patients included in Turkey were not to be younger than 3 years.
3	03-January-2013	After	France	• Change in exclusion criteria 13. • Clarification regarding major surgery.
4	Not applicable ^a	After	Global	Superseded by version 2.0.
4	04-July-2013	After	Global	<u>Major change:</u> Change of the planned patient tailored nonacog beta pegol dose in the extension phase to a fixed dose of 40 IU/kg once weekly. <u>Minor Changes:</u> • List of participating countries updated. • Addition of pre-dose FIX activity measurements in the extension phase of the trial to provide pharmacokinetic information. • The number of post-dose FIX measurements was reduced to minimise the burden of the patients by less venipunctures. • A more comprehensive safety surveillance in terms of immunogenicity (i.e. anti-drug antibodies) was implemented. In addition if a

Amendment number	Issue date	Timing of change (before/after FPFV)	Countries affected	Key changes
				patient developed binding antibodies against nonacog beta pegol, the patient was asked to have a PK session performed at the earliest convenience. This implied five additional visits to the clinic. • If needed, use of recombinant factor VIIa for treatment of bleeds in low responding inhibitor patients was allowed for up to 4 weeks. FIX containing bypassing agents were not allowed as the effect on the inhibitor formation was unknown. • A change in interim analysis was made in order to perform an interim analysis in association with Marketing Authorisation Application or upon request from Health Authorities.
5	15-July-2014	After	Global	• Major surgery could be performed as part of the trial to allow the patients to continue with nonacog beta pegol treatment and avoid withdrawal. • All patients were switched from the current nonacog beta pegol to nonacog beta pegol intended for commercial use. For this reason additional blood samples for immunogenicity testing (antibody measurements/HCP) were to be drawn. • Optional blood samples for potential future assessments ("biospecimens for storage") were drawn to address safety or efficacy, anti-drug antibody assessments and to improve the understanding of the mechanisms of action.
6	12-January-2015	After	Global	• Total blood volume drawn at each visit in the extension phase was corrected from 5 mL to 9-11 mL. • Bio specimen for storage for genotype was added to flowchart. • Due to high FIX trough levels, a heat treatment step is included prior to the Nijmegen modified FIX Bethesda assay. • If the first inhibitor test is positive, a sample for lupus anticoagulant was taken in conjunction with the second confirmatory inhibitor sample" added. • Clarification of interim drug dispensing visit for home treatment was halfway (every 3rd month) between each scheduled 6 months assessment visit. • Additional assessment visit took place between visit 15 and visit 17 depending on how far the individual patient was in the trial and corresponded to visit 16 in terms of assessments and measurements. This

Amendment number	Issue date	Timing of change (before/after FPFV)	Countries affected	Key changes
				additional visit coincided with the interim drug dispensing visits. • Clarification of measurement of FIX activity performed at a local laboratory and the use of nonacog beta pegol reference standard. • All patients needed to complete PRO questionnaires at visit 17. Furthermore, patients who moved out of their original age group were asked to complete an additional questionnaire for their current age group • Timelines changed (LPLV changed to 31 October 2018).
7 ^a	17-October-2016	After	Global	• Global amendment no. 7 was retracted from submission to health authorities, since the wording of the reconstituted drug product colour was not aligned with the drug product specification as intended. The colour of the reconstituted drug product is changed to "clear to almost clear and colourless solution". • Exemptions from categorisation ("normal", "out of normal range, not clinically significant" or "out of normal range, clinically significant") of clinical significance in laboratory parameters (FIX activity, activated partial thromboplastin time (aPTT), FIX inhibitors, binding non-neutralising nonacog beta pegol/FIX antibodies, HCP antibodies, allergic reaction testing and F9 genotype testing) as these results were a reflection of the underlying disease and the treatment. These changes were implemented in protocol amendment 8.
8	05-December-2016	After	Global	• Update in the colour of the nonacog beta pegol drug product. The appearance of the reconstituted solution was updated to "a clear and colourless solution free from clearly visible particles" in alignment with the CMC document "Handling Instruction N7999 nonacog beta pegol" which is compliant with the Product Specification." • Elaboration to the allergic reaction testing to align with the already described procedure in the flowchart.
9	16-November-2017	After	Global	Superseded by version 2.0
9	01-December-2017	After	Global	• Measurement of PEG in plasma (including leftovers from already collected plasma samples), urinalysis, additional neurological assessments as part of the physical examination and inclusion of eGFR analysis in biochemistry were added at every

Amendment number	Issue date	Timing of change (before/after FPFV)	Countries affected	Key changes
				prospective visit to investigate the clinical effects of long term exposure of nonacog beta pegol in choroid plexus, liver and kidney • Retrospective collection of height measured at visit 11. • All central nervous system (CNS)- related events were categorised as MESIs to fully monitor potential neurological adverse events. • The LPLV of the trial was extended to 2023 to allow the patients to continue up to visit 32 and the youngest child to reach up to 12 years of age. • New (and additional) age-appropriate PRO introduced at visit 17 and repeated at End of trial (EOT). Adult patients were asked to consent to their parents/LAR filling in the same questionnaire as the parent filled in at visit 17. • Shipment of drug from site/pharmacy to patient's home for selected countries. • The monitoring visit frequency was prolonged to every 28 weeks and a phone call or other contact between parents and site staff was allowed. • Definition of incremental recovery was clarified. Update of terminology of auxiliary supplies was updated. Text regarding technical complaints was updated to reflect new processes.
10	27-June-2018	After	Global	• Addition of neurocognitive assessments in the protocol. • Renal adverse events were categorised as MESIs • Patient reported outcomes (PRO) were added at visits 22/23/24 (the relevant visit where neurocognitive assessments are performed for the first time in each patient) and performed at end-of-trial visit. • The chromogenic assay was no longer used by the central laboratory

*Local amendment withdrawn prior to HA approval.

Protocol deviations

Protocol deviations (PDs) were categorised as important or non-important. Important PDs were deviations that could significantly impact the completeness, accuracy and/or reliability of the trial data or that could significantly affect the subject's rights, safety or well-being. A total of 306 important PDs were reported in this trial of which 1 was country-level, 6 were trial level, 38 were at trial site level and 261 were patient level PDs. None of the PDs were considered to have an overall impact on the trial conduct, subject safety or data interpretation.

In 2018, Novo Nordisk started following Drug Information Association (DIA) categorisation for reporting PDs. In this trial, PDs reported before 01 January 2019 were categorised according to Novo Nordisk PD categorisation and PDs reported after 01 January 2019 were categorised according to DIA PD categorisation. Hence, the current CTR includes all PDs categorised per these two different categorisation methods.

Table 8: Summary of important protocol deviations at trial site and patient level

Protocol deviation category	Site-level (count of PDs)	Patient-level (count of PDs)
DIA categories		
Concomitant medication	-	-
Inclusion/Exclusion criteria	-	-
Informed consent	-	-
SAE notification/Safety procedure	-	1
Subject visit schedule	-	1
Treatment Administration	-	6
Trial procedures/Assessment	-	6
NN categories		
Informed consent	1	5
Protocol Deviation- Informed consent		14
PD Imp- Informed consent		
Inclusion/exclusion/randomisation/withdrawal criteria	1	3
Trial product/drug handling	6	42
Treatment compliance	1	65
Assessment deviations		86
PD Imp- assessment deviations (including lab)		4
Protocol deviation- assessment deviation		8
Protocol deviation – lab samples	1	
Other		
PD Imp- other	24	16
Protocol deviation- other	1	3
Visit window	3	1
Total	38	261

Abbreviations: Imp = important; PD = protocol deviation;

Baseline data

Table 9: Baseline demographics and body measurements (FAS)

	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
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)
Body weight (kg)			
N	12	13	25
Mean (SD)	17.3 (4.2)	37.0 (10.0)	27.5 (12.6)
Median	17.1	34.8	25.2
Min ; Max	10.6 ; 25.2	21.0 ; 60.0	10.6 ; 60.0
Height (cm)			
N	12	13	25
Mean (SD)	100.1 (13.3)	141.1 (12.1)	121.4 (24.3)
Median	100.0	140.0	125.0
Min ; Max	77.0 ; 125.0	116.1 ; 162.0	77.0 ; 162.0
BMI (kg/m^2)			
N	12	13	25
Mean (SD)	17.0 (1.7)	18.0 (2.1)	17.5 (2.0)
Median	17.0	17.5	17.5
Min ; Max	14.7 ; 21.1	15.3 ; 23.3	14.7 ; 23.3

The baseline value for height is the measurement at screening visit 1.

The baseline value for weight is the value from visit 2.

If the visit 2 value for weight was missing, the value from visit 1 was used as baseline.

BMI: body mass index.

Haemophilia and treatment history

Of the 25 patients, 20 patients had a FIX level <1.0%, 2 patients had FIX level <0.6%, 2 patients had 1.0% FIX level and 1 patient had FIX level of 1.2%. The majority of the patients (16 patients; 64.0%) did not have a family history of haemophilia B. All patients were previously treated patients with a history of at least 50 EDs (mean=346.3 EDs) to other FIX products and no history of inhibitors. Prior to the enrolment in the trial, the majority of the patients (22 out of 25 patients; 88.0%) were on prophylaxis regimen either with recombinant FIX product (20 patients) or on plasma-derived products (2 patients) and were treated for an average of 56.4 months. The median number of treatment-requiring bleeds within the last 12 months for previous prophylaxis patients was 2.0. Few patients (3 out of 25 patients; 12.0%) were on on-demand treatment prior to enrolment in the trial with either recombinant FIX product (1 patient) or plasma derived products (2 patients). The patients were on on-demand treatment for an average of 96.7 months. The median number of treatment-requiring bleeds within the last 12 months for patients previously on on-demand treatment was 9.0.

Table 10: Haemophilia and inhibitor history and treatment history - FAS

	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)
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)
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)
Current treatment prior to trial, N (%)			
N	12 (100.0)	13 (100.0)	25 (100.0)
Prophylaxis regimen	11 (91.7)	11 (84.6)	22 (88.0)
On-demand	1 (8.3)	2 (15.4)	3 (12.0)
<u>Previous prophylaxis patients:</u>			

Months on prophylaxis			
N	11	11	22
Mean (SD)	22.4 (18.5)	90.5 (31.6)	56.4 (43.0)
Median	14.0	86.0	46.5
Min : Max	5 : 72	33 : 140	5 : 140
Bleeds within the last 12 months****			
Treatment requiring			
N	9	11	20
Mean (SD)	3.0 (3.1)	2.7 (3.2)	2.9 (3.1)
Median	2.0	2.0	2.0
Min : Max	0 : 9	0 : 9	0 : 9
Common dose level (U/kg)			
N	11	11	22
Mean (SD)	45.6 (11.5)	61.5 (31.9)	53.5 (24.8)
Median	50.0	50.0	50.0
Min : Max	22 : 62	24 : 110	22 : 110
<u>Previous on-demand patients:</u>			
Months on on-demand			
N	1	2	3
Mean (SD)	37.0 (0)	126.5 (23.3)	96.7 (54.2)
Median	37.0	126.5	110.0
Min : Max	37 : 37	110 : 143	37 : 143

```

Bleeds within the last 12 months
Treatment requiring
  N              1              2              3
  Mean (SD)      17.0 (0)      7.0 ( 2.8)    10.3 ( 6.1)
  Median         17.0          7.0           9.0
  Min : Max      17 : 17        5 : 9         5 : 17

Dose level (U/kg)+
  N              1              2              3
  Mean (SD)      2000 (0)      30.0 ( 0.0)    686.7 ( 1137)
  Median         2000          30.0           30.0
  Min : Max      2000 : 2000    30 : 30        30 : 2000

ED (all patients):
-----
Exposure days prior to trial*****
  N              12              13              25
  Mean (SD)      145.4 (108.4)    531.7 (348.0)    346.3 (323.6)
  Median         99.0           544.0           226.0
  Min : Max      53 : 399        50 : 999        50 : 999

```

* 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.
 **** If less than 12 months on on-demand, the annual number of bleeds has been set to missing.
 ***** Must be at least 50 exposures to comply with inclusion criteria number 5.
 An exposure day (ED) is defined as a day where at least one dose is given.
 + One subject registered 2000 (U/kg) as dose level, this is a data issue where the subject might mistakenly reported units (U) instead of (U/kg).

Numbers analysed

Exposure

Table 11: Exposure days and years in trial by actual age groups - FAS

	0-6 year age group	7-12 year age group	13-17 year age group	18-70 year age group	Total
Number of patients	12	23	12	3	25
Exposure days	1815	3944	2029	136	7924
Years in trial	34.20	74.73	38.72	3.23	150.87
Mean treatment period (years)	2.85	3.25	3.23	1.08	6.03

All evaluations of safety were based on the SAS, including all 25 dosed patients thus being equal to FAS.

Outcomes and estimation

Annualised bleeding rate (ABR)

Table 12: Annualised bleeding rate by actual age group – FAS

	Younger children (0-6 years)	Older children (7-12 years)	Adolescents (13-17 years)	Adults (18-70 years)	Total
Total bleeds					
Number of patients	12	23	12	3	25
Patients with bleeds, N (%)	7 (58.3)	16 (69.6)	7 (58.3)	1 (33.3)	20 (80.0)
Number of bleeds	35	63	29	1	128
Median ABR (IQR)	0.55 (0.00; 1.31)	0.52 (0.00; 2.02)	0.21 (0.00; 0.81)	0.00 (0.00; 1.60)	0.50 (0.25; 1.65)
Poisson-estimated ABR [95% CI]	1.02 [0.68; 1.54]	0.84 [0.41; 1.75]	0.75 [0.41; 1.36]	0.31 [-; -]	0.85 0.51; 1.40
Spontaneous bleeds					
Number of patients	12	23	12	3	25
Patients with bleeds, N (%)	3 (25.0)	6 (26.1)	4 (33.3)	1 (33.3)	9 (36.0)
Number of bleeding episodes	7	17	15	1	40
Median ABR (IQR)	0.00 (0.00; 0.20)	0.00 (0.00; 0.17)	0.00 (0.00; 0.40)	0.00 (0.00; 1.60)	0.00 (0.00; 0.25)
Poisson-estimated ABR [95% CI]	0.20 [0.09; 0.47]	0.23 [0.05; 0.96]	0.39 [0.17; 0.89]	0.31 [-; -]	0.27 [0.13; 0.56]
Traumatic bleeds					
Number of patients	12	23	12	3	25
Patients with bleeds, N (%)	7 (58.3)	14 (60.9)	7 (58.3)	0 (0.0)	19 (76.0)
Number of bleeding episodes	28	42	14	0	84
Median ABR (IQR)	0.53 (0.00; 0.87)	0.33 (0.00; 1.18)	0.21 (0.00; 0.45)	0.00 (0.00; 0.00)	0.38 (0.13; 0.69)
Poisson-estimated ABR [95% CI]	0.82 [0.55; 1.23]	0.56 [0.25; 1.27]	0.36 [0.24; 0.54]	- [-; -]	0.56 [0.31; 1.00]

Note: Age groups are based on actual age, therefore some patients are represented in multiple columns.

Abbreviations: ABR = annualised bleeding rate; CI = confidence interval; IQR = interquartile range; N = total number of patients

Mean ABR stratified by previous treatment (prophylaxis or on demand) and compared with historical ABRs were:

- 0.78 versus historical ABR of 2.70 (patients previously treated with prophylaxis)
- 1.55 versus historical ABR of 10.33 (patients previously treated with on demand treatment)

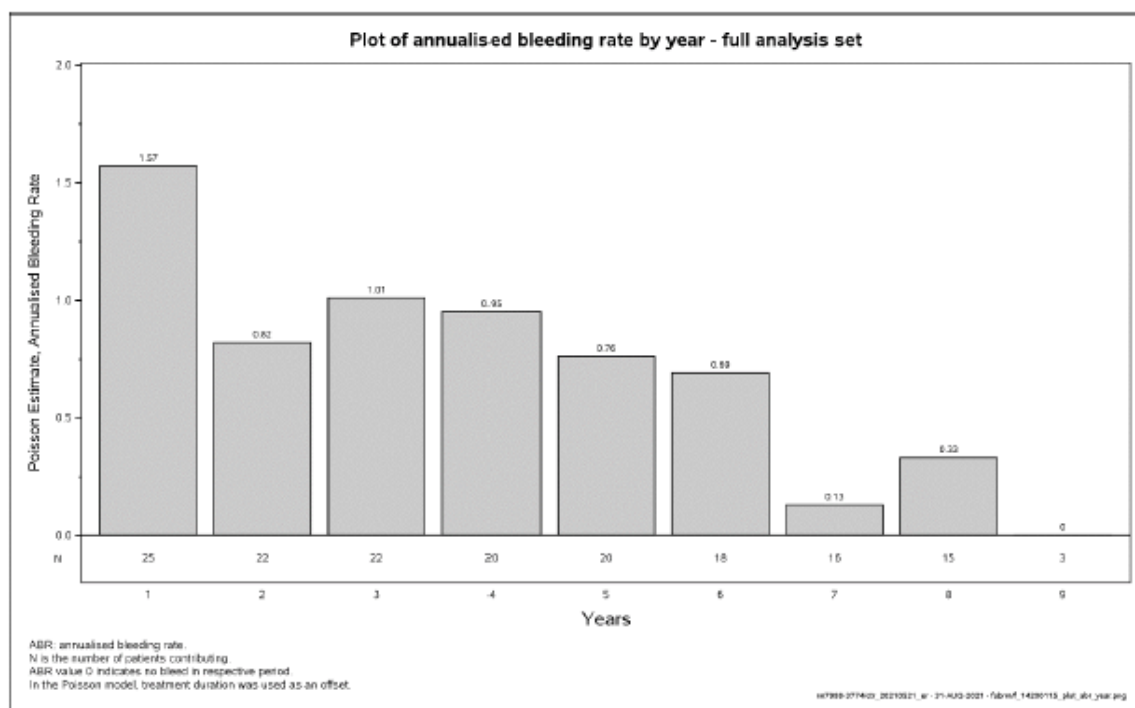


Figure 10: Plot of annualised bleeding rate by year - FAS

Target joints

Two (2) patients had pre-existing target joints at baseline. During the main phase of the trial, both target joints were considered resolved based upon ISTH criteria. No patient developed new target joint(s) during the trial, according to ISTH criteria.

Haemostatic effect

Table 13: Haemostatic response by actual age group - FAS

	Younger children (0-6 years)	Older children (7-12 years)	Adolescents (13-17 years)	Adults (18-70 years)	Total
Total bleeds					
Number of patients	12	23	12	3	25
Number of patients with bleeds, N (%)	7 (58.3)	16 (69.6)	7 (58.3)	1 (33.3)	20 (80.0)
Number of bleeds	35	63	29	1	128
Haemostatic success rate, N (%)	31 (88.6)	59 (93.7)	23 (79.3)	1 (100.0)	114 (89.1)
Spontaneous bleeds					
Number of patients	12	23	12	3	25
Number of patients with bleeds, N (%)	3 (25.0)	6 (26.1)	4 (33.3)	1 (33.3)	9 (36.0)
Number of bleeds	7	17	15	1	40
Haemostatic success rate, N (%)	6 (85.7)	16 (94.1)	11 (73.3)	1 (100.0)	34 (85.0)
Traumatic bleeds					
Number of patients	12	23	12	3	25
Number of patients with bleeds, N (%)	7 (58.3)	14 (60.9)	7 (58.3)	0 (0.0)	19 (76.0)
Number of bleeds	28	42	14	0	84
Haemostatic success rate, N (%)	25 (89.3)	39 (92.9)	12 (85.7)	0 (0.0)	76 (90.5)

Note: Age groups are based on actual age, therefore some patients are represented in multiple columns.

The success rate for patients who previously had been on prophylaxis treatment was 90.6% as compared to 81.8% for patients who had been on on-demand treatment before enrolment to the present trial.

Nonacog beta pegol consumption

Table 14: Actual consumption of nonacog beta pegol by actual age group - FAS

	Younger children (0-6 years)	Older children (7-12 years)	Adolescents (13-17 years)	Adults (18-70 years)	Total
Consumption used for treatment^a per year per patient^b (IU/kg/year)					
N	12	23	12	3	25
Mean (SD)	2208.6 (78.8)	2324.8 (83.3)	2271.6 (137.0)	1819.8 (798.0)	2270.4 (111.3)
Median	2223.1	2322.9	2268.1	2232.8	2277.8
Min; Max	2015.1; 2312.3	2120.6; 2466.8	2004.4; 2517.5	899.9; 2326.6	2015.1; 2512.4
Average prophylaxis dose^c (IU/kg)					
N	1768	3864	1975	135	7742
Mean (SD)	42.0 (1.6)	43.7 (1.8)	43.2 (1.0)	42.4 (0.4)	43.2 (1.7)
Median	41.9	44.0	43.2	42.5	43.2
Min; Max	14.3; 56.0	6.4; 49.6	39.2; 47.7	41.8; 43.2	6.4; 56.0
Average dose for treatment of bleed from start to stop of bleed^d (IU/kg/bleed)					
N	35	63	29	1	128
Mean (SD)	53.6 (32.2)	50.6 (20.4)	88.6 (115.1)	42.6 (-)	60.0 (60.4)
Median	42.2	43.2	43.8	42.6	43.1
Min; Max	21.9; 213.4	26.7; 136.0	41.2; 569.3	42.6; 42.6	21.9; 569.3
Number of injections of nonacog beta pegol per bleed, N (%)					
1-2 injections	34 (97.1)	61 (96.8)	24 (82.8)	1 (100.0)	120 (93.8)

Abbreviation: SD = standard deviation; Age groups are based on actual age, therefore some patients are represented in multiple columns.

^a Consumption used for treatment includes all doses given (prophylaxis, treatment of bleed, minor and major surgery and PK)

^b N is number of patients

^c N is number of doses

^d N is number of bleeds

Table 15: Number of injections of nonacog beta pegol per bleed by actual age - FAS

	Younger children (0-6 years)	Older children (7-12 years)	Adolescents (13-17 years)	Adults (18-70 years)	Total
Number of patients	12	23	12	3	25
Number of patients with bleeds, N (%)	7 (58.3)	16 (69.6)	7 (58.3)	1 (33.3)	20 (80.0)
Number of patients with 0 bleeds, N(%)	5 (41.7)	7 (30.4)	5 (41.7)	2 (66.7)	5 (20.0)
Number of bleeds	35	63	29	1	128
Number of injections to treat the bleed*, N (%)					
N	35 (100.0)	63 (100.0)	29 (100.0)	1 (100.0)	128 (100.0)
1 injection	29 (82.9)	53 (84.1)	22 (75.9)	1 (100.0)	105 (82.0)
2 injections	5 (14.3)	8 (12.7)	2 (6.9)	-	15 (11.7)
3 injections	-	2 (3.2)	2 (6.9)	-	4 (3.1)
5 injections	1 (2.9)	-	-	-	1 (0.8)
7 injections	-	-	2 (6.9)	-	2 (1.6)
12 injections	-	-	1 (3.4)	-	1 (0.8)
N	35	63	29	1	128
Mean (SD)	1.3 (0.7)	1.2 (0.5)	2.0 (2.5)	1.0 (-)	1.4 (1.3)
Median	1.0	1.0	1.0	1.0	1.0
Min : Max	1.0 : 5.0	1.0 : 3.0	1.0 : 12.0	1.0 : 1.0	1.0 : 12.0

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

Age groups are based on actual age, therefore some patients are represented in multiple columns.

Results separated by main and extension phase

Table 16: Detail of bleeds and annualised bleeding rate by actual age groups for main and extension phase – FAS

	Main phase			Extension phase		
	0-6 years	7-12 years	Total (%)	0-6 years	7-12 years	Total (%)
Number of Patients	12	14	25	10	20	21
Number of patients with bleeds, N (%)	5 (41.7)	10 (71.4)	15 (60.0)	4 (40.0)	10 (50.0)	11 (52.4)
Number of patients with 0 bleeds, N (%)	7 (58.3)	4 (28.6)	10 (40.0)	6 (60.0)	10 (50.0)	10 (47.6)
Number of bleeds	10	27	37	25	36	61
Cause of bleed, N (%)						
N	10 (100.0)	27 (100.0)	37 (100.0)	25 (100.0)	36 (100.0)	61 (100.0)
Spontaneous	2 (20.0)	8 (29.6)	10 (27.0)	5 (20.0)	9 (25.0)	14 (23.0)
Traumatic	8 (80.0)	15 (55.6)	23 (62.2)	20 (80.0)	27 (75.0)	47 (77.0)
Other	-	4 (14.8)	4 (10.8)	-	-	-
Re-bleed, N (%)						
N	10 (100.0)	27 (100.0)	37 (100.0)	25 (100.0)	36 (100.0)	61 (100.0)
Yes	1 (10.0)	1 (3.7)	2 (5.4)	-	1 (2.8)	1 (1.6)
No	9 (90.0)	26 (96.3)	35 (94.6)	25 (100.0)	35 (97.2)	60 (98.4)
Location of bleed and cause, N (%)						
N	10 (100.0)	27 (100.0)	37 (100.0)	25 (100.0)	35 (100.0)	60 (100.0)
Gastrointestinal, traumatic	-	1 (3.7)	1 (2.7)	-	-	-
CNS, traumatic	-	-	-	1 (4.0)	-	1 (1.7)
Joint, spontaneous	-	5 (18.5)	5 (13.5)	1 (4.0)	6 (17.1)	7 (11.7)
Joint, traumatic	2 (20.0)	6 (22.2)	8 (21.6)	8 (32.0)	11 (31.4)	19 (31.7)
Mucosal, other	-	4 (14.8)	4 (10.8)	-	-	-
Mucosal, spontaneous	1 (10.0)	-	1 (2.7)	1 (4.0)	2 (5.7)	3 (5.0)
Mucosal, traumatic	1 (10.0)	1 (3.7)	2 (5.4)	3 (12.0)	-	3 (5.0)

Muscular, spontaneous	-	2 (7.4)	2 (5.4)	1 (4.0)	-	1 (1.7)
Muscular, traumatic	1 (10.0)	3 (11.1)	4 (10.8)	-	9 (25.7)	9 (15.0)
Other, spontaneous	-	1 (3.7)	1 (2.7)	-	1 (2.9)	1 (1.7)
Other, traumatic	1 (10.0)	1 (3.7)	2 (5.4)	1 (4.0)	2 (5.7)	3 (5.0)
Skin, traumatic	-	-	-	-	3 (8.6)	3 (5.0)
Subcutaneous, spontaneous	1 (10.0)	-	1 (2.7)	2 (8.0)	-	2 (3.3)
Subcutaneous, traumatic	3 (30.0)	3 (11.1)	6 (16.2)	7 (28.0)	1 (2.9)	8 (13.3)
Classification of bleed, N (%)						
N	10 (100.0)	27 (100.0)	37 (100.0)	25 (100.0)	36 (100.0)	61 (100.0)
Mild/moderate	10 (100.0)	27 (100.0)	37 (100.0)	25 (100.0)	36 (100.0)	61 (100.0)
Time since last dose*, N (%)						
N	10 (100.0)	18 (100.0)	28 (100.0)	21 (100.0)	27 (100.0)	48 (100.0)
≤4 days	2 (20.0)	7 (38.9)	9 (32.1)	12 (57.1)	13 (48.1)	25 (52.1)
>4 days	8 (80.0)	11 (61.1)	19 (67.9)	9 (42.9)	14 (51.9)	23 (47.9)
All bleeds, Individual ABRs						
N	12	14	25			
Median (Interquartile range)	0.00 (0.00; 1.99)	2.00 (0.00; 3.02)	1 (0.00; 2.90)	0.00 (0.00; 1.65)	0.15 (0.00; 1.29)	0.30 (0.00; 1.39)
Poisson estimate of ABR (95% CI)	0.97 (0.50; 1.89)	2.10 (1.34; 3.30)	1.60 (1.07; 2.38)	1.05 (0.65; 1.69)	0.58 (0.21; 1.64)	0.71 (0.35; 1.45)
Spontaneous bleeds, Individual ABRs						
N	12	14	25	10	20	21
Median (Interquartile range)	0.00 [0.00; 0.00]	0.00 [0.00; 0.97]	0.00 [0.00; 0.00]	0.00 [0.00; 0.00]	0.00 [0.00; 0.00]	0.00 [0.00; 0.00]
Poisson estimate of ABR (95% CI)	0.19 [0.06; 0.65]	0.62 [0.23; 1.68]	0.43 [0.19; 1.01]	0.21 [0.09; 0.50]	0.15 [0.02; 1.28]	0.16 [0.03; 0.78]
Traumatic bleeds, Individual ABRs						
N	12	14	25	10	20	21
Median (Interquartile range)	0.00 [0.00; 1.48]	0.98 [0.00; 1.93]	0.97 [0.00; 1.93]	0.00 [0.00; 1.05]	0.00 [0.00; 0.70]	0.00 [0.00; 0.70]
Poisson estimate of ABR (95% CI)	0.78 [0.40; 1.51]	1.17 [0.65; 2.09]	0.99 [0.63; 1.56]	0.84 [0.51; 1.36]	0.44 [0.14; 1.38]	0.55 [0.25; 1.21]
Abbreviation: CNS = central nervous system; ABR = Annualised bleeding rate * Only calculated if complete time points are available. Duration is only calculated if both start and stop time of bleed is reported. Only primary location is summarised. Age groups are based on actual age, therefore some patients are represented in multiple columns. 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. Table reflects the data available till interim DLP cut-off date 25 November 2020.						
Cross-reference: Modified from Appendix 2, Tables 1 to 8						

Table 17: Actual consumption of nonacog beta pegol by actual age groups for main and extension phase – FAS

	Main phase			Extension phase		
	Younger children (0 - 6 years)	Older children (7 - 12 years)	Total	Younger children (0 - 6 years)	Older children (7 - 12 years)	Total
Number of Patient	12	14	25	10	20	21
Consumption used for treatment ^a per year per patient ^b (IU/kg/year)						
N	12	14	25	10	20	21
Mean (SD)	2228.1 (128.3)	2389.7 (101.1)	2320.8 (134.9)	2230.9 (52.6)	2288.6 (144.8)	2271.8 (138.8)
Median	2203.6	2389.5	2350.9	2224	2314.8	2298.6
Min; Max	2015.1; 2458.5	2165.7; 2532.4	2015.1; 2532.4	2159.7; 2313.7	1758.3; 2449.2	1758.3; 2449.2
Average prophylaxis dose ^c (IU/kg)						
N	536	672	1208	1232	3192	4424
Mean (SD)	42.2 (2.1)	43.7 (2.2)	43.0 (2.3)	41.9 (1.4)	43.7 (1.8)	43.2 (1.9)
Median	42.1	44.3	43.1	41.9	44	43.3
Min; Max	14.3; 56.0	32.6; 49.6	14.3; 56.0	38.3; 50.0	6.4; 48.7	6.4; 50.0
Average dose for minor surgery ^c (IU/kg)						
N	0	0	0	5	6	11
Mean (SD)	- (-)	- (-)	- (-)	41.2 (1.0)	47.3 (7.4)	44.5 (6.1)
Median	-	-	-	40.6	45.8	42.8
Min ; Max	- ; -	- ; -	- ; -	40.5; 42.8	40.6; 61.5	40.5; 61.5
Average dose for major surgery ^c (IU/kg)						
N	0	0	0	0	2	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 ^d (IU/kg/bleed)						
N	10	27	37	25	36	61
Mean (SD)	61.4 (55.6)	48.4 (14.3)	51.9 (30.9)	50.5 (16.6)	52.2 (24.1)	51.5 (21.2)
Median	42.6	44.5	43.2	42.1	42.8	42.6
Min; Max	21.9; 213.4	26.7; 80.9	21.9; 213.4	39.7; 84.6	37.2; 136.0	37.2; 136.0
Number of days between doses ^{e,f}						
N	524	659	1183	1222	3181	4403
Mean (SD)	7.0 (0.7)	7.0 (0.8)	7.0 (0.7)	7.1 (0.6)	7.1 (0.9)	7.1 (0.9)
Median	7	7	7	7	7	7
Min; Max	1.0; 13.0	1.0; 14.0	1.0; 14.0	5.0; 14.0	1.0; 23.0	1.0; 23.0
Abbreviations: SD = standard deviation; Max = maximum; Min = minimum ^a Consumption used for treatment includes all doses given (prophylaxis, treatment of bleed, minor and major surgery and PK). ^b N is number of patients ^c N is number of doses. ^d N is number of bleeds. ^e Only count prophylaxis doses except the first prophylaxis dose. Age groups are based on actual age, therefore some patients are represented in multiple columns Table reflects the data available till interim DLP cut-off date on 25 November 2020						

Cross-reference: Modified from Appendix 2, Tables 11 and 12

Surgeries

A total of 12 doses were taken in relation to the 17 **minor surgeries** in 10 patients, and the mean dose level was 44.4 IU/kg. One patient underwent a **major surgery** for arteriovenous fistula and received two doses of 41.8 IU/kg, where one dose was taken within 1 hour prior to the surgery and the other dose was taken 2 days after the surgery to consolidate the haemostatic effect, in compliance with the protocol-defined dose for major surgery (80 IU/kg).

Table 18: Major surgeries during trial 3774 - FAS

Description of surgery	Indication	Surgery start datetime/ Surgery end datetime	Impf	Datetime of preventive dose	Haemostatic response
Arteriovenous fistula closure	Fistula closure because venous access is now available	13JUN18:12:10:00/ 13JUN18:13:00:00		13JUN2018:11:27	EXCELLENT

Table 19: Minor surgeries during trial 3774 - FAS

Description of surgery	Indication	Surgery start datetime/ Surgery end datetime	Impf	Datetime of preventive dose	Haemostatic response
Port a cath removal	non-functional port-a-cath, no longer needed	23JUL14:11:54:00/ 23JUL14:13:43:00		23JUL2014:10:54	
Extraction of teeth #8s and #9s	Impacted supernumerary teeth	30MAR15:13:15:00/ 30MAR15:13:33:00		30MAR2015:11:22	
Extraction of L5 (left upper molar)	Exfoliation	23SEP14:15:00:00/ 23SEP14:15:35:00		23SEP2014:14:22	
Bronchoscopy	Haemoptysis for investigation	04MAR16:09:50:00/ 04MAR16:10:00:00		04MAR2016:08:00	
tooth extraction	baby tooth removal	10MAY13:14:00:00/ 10MAY13:14:30:00			
removal of 2 teeth	teeth removal	25NOV13:10:00:00/ 25NOV13:12:00:00		20NOV2013:07:45	
Correction of nasal deviation	Fractured nose	19DEC13:16:39:00/ 19DEC13:16:56:00		19DEC2013:12:08	
Tooth removed	Abscess tooth	10JAN17:14:45:00/ 10JAN17:15:00:00		08JAN2017:12:00	
Myringotomy and grommet insertion	Glue ear	09MAR15:10:00:00/ 09MAR15:10:23:00		09MAR2015:09:30	
Portacath removal	Infected portacath	18MAY15:12:00:00/ 18MAY15:00:00:00	H/	18MAY2015:--:--	
PortaCath insertion	To infuse regular clotting factor	24JUN15:12:00:00/ 24JUN15:00:00:00	H/	24JUN2015:--:--	
Grommets	Left ear infection	29MAR17:12:00:00/ 29MAR17:00:00:00	H/	29MAR2017:--:--	
Deciduous tooth extraction	Deciduous tooth extraction	14NOV14:15:52:00/ 14NOV14:16:19:00			
Deciduous tooth extraction	Deciduous tooth extraction	01APR16:17:00:00/ 01APR16:18:00:00			
Deciduous tooth extraction	Deciduous tooth extraction	08APR16:15:50:00/ 08APR16:16:30:00			
gingival flap excision	gingival flap excision	08APR16:15:50:00/ 08APR16:16:30:00			
Tooth extraction	Baby tooth removal	05APR14:10:30:00/ 05APR14:10:45:00			

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

Patient-reported outcomes and health economic impact

No clear trends in PROs (HAEMO-QOL, TAPQOL, HEMO-SAT) were observed, as the number of questionnaires received was insufficient to draw conclusions (0-3 years: 6 questionnaires; 4-7 years: 3 children and 4 parent questionnaires; 8-12 years: 8 questionnaires each, children and parents). Results from the health economic endpoints indicated that none of the patients reported any intensive care hospitalisation days, most (83.3%) patients did not miss any days of school during the study due to bleeds, and parents of patients missed an average of 0.4 days of work due to bleeds.

Trial ID: NN7999-3895

Safety and Efficacy of NNC-0156-0000-0009 (Nonacog beta pegol) in Previously Untreated Patients with Haemophilia B

An open-label single-arm multicentre non-controlled phase 3a trial investigating safety and efficacy of nonacog beta pegol (N9-GP) in prophylaxis and treatment of bleeding episodes in previously untreated patients with haemophilia B (FIX activity $\leq 2\%$).

Methods

Study participants

Inclusion criteria

For an eligible subject, all inclusion criteria must be answered "yes".

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male, age < 6 at the time of signing informed consent.
3. Patients with the diagnosis of haemophilia B (FIX activity level $\leq 2\%$) based on medical records or central laboratory results.
4. Previously untreated or exposed to FIX containing products less than or equal to 3 EDs (5 previous exposures to blood components is acceptable).

Exclusion criteria

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

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

Treatments

Pre-prophylaxis: 40 IU/kg (or 80 IU/kg for a severe bleed) on demand or intervals longer than once weekly

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)

Objectives

Primary Objective

- To evaluate immunogenicity of N9-GP (nonacog beta pegol)

Secondary Objectives

- To evaluate safety of N9-GP (nonacog beta pegol)
- To evaluate efficacy of N9-GP (nonacog beta pegol)
 - in long-term prophylaxis treatment
 - in the treatment of bleeding episodes
 - through the surrogate marker: FIX activity
 - through monitoring of number of doses and consumption of N9-GP

Outcomes/endpoints

Primary endpoint

- Incidence of inhibitory antibodies against FIX

Secondary endpoints

- Number and frequency of adverse events (AEs), serious AEs (SAEs) and Medical Events of Special Interest (MESI)
- Number of breakthrough bleeding episodes during prophylaxis (annualised bleeding rate)
- Haemostatic effect by 4-point haemostatic response scale ("excellent", "good", "moderate" and "poor")
- Incremental recovery at 30 minutes (IR30min), FIX activity at 30 minutes (C30min) and trough level
- Amount of drug administered and number of doses needed to treat a bleeding episode

Sample size

No formal sample size calculations have been performed. The sample size of 40 completers is based on EMA guideline. A total of 60 patients were planned to be screened, 50 patients to be enrolled and 40 patients were expected to complete the trial.

Randomisation

No randomisation was performed due to the single-arm nature of both submitted paediatric trials (NN7999-3895).

Blinding (masking)

Blinding does not apply as both submitted paediatric trials (NN7999-3774 and NN7999-3895) were open-label trials

Statistical methods

Descriptions and analysis of efficacy will be based on the Full Analysis Set (FAS), as defined in ICH E9 guidelines. The FAS includes all patients exposed to N9-GP. The safety analysis and descriptions will be based on the Safety Analysis Set (SAS). The SAS will consist of all patients exposed to N9-GP.

Safety: The primary endpoint was a safety endpoint defined as incidence of inhibitory antibodies against FIX. The rate of inhibitory antibodies was reported and a 1-sided 97.5% upper confidence limit was provided based on an exact calculation for a binomial distribution. For the calculation of the rate the numerator included the patients with inhibitors, while the denominator included all patients with a minimum of 10 exposure days plus any patient with less than 10 exposure days but with inhibitors.

Efficacy: The first supportive secondary endpoint was number of bleeding episodes during prophylaxis. Annualised bleeding rate was summarised and a 95% two-sided confidence interval was provided based on the negative binomial regression model with breakthrough bleeding episodes as the outcome variable, and adjusting for exposure time. The haemostatic effect of nonacog beta pegol was summarised and listed according to the four-point scale for haemostatic response (poor, moderate, good and excellent). A success rate was calculated based on counting good or excellent as successes and poor and moderate as failures, and was based only on reported outcomes. FIX trough level was defined as the activity recorded immediately before nonacog beta pegol injection was given and reported as IU/mL. IR30min was defined as the rise in FIX activity per IU/kg administered and was recorded 30 minutes after the end of nonacog beta pegol injection, and reported as [IU/mL]/[IU/kg]. It was calculated as the baseline adjusted FIX activity recorded 30 minutes after ended nonacog beta pegol injection and dividing the administered dose (IU/kg body weight (bw)). Amount of nonacog beta pegol used for prophylaxis (IU/Kg/month/year) and amount consumed per bleeding episode (number of doses and IU/kg bw/bleeding episode) was summarised and listed.

Results

Participant flow

At interim cut-off, 55 patients were screened and 50 of these were dosed with nonacog beta pegol. Of the 50 exposed patients, 39 patients (78%) completed the main phase, and 33 patients (66%) completed the extension phase. Six (6) patients completed the trial.

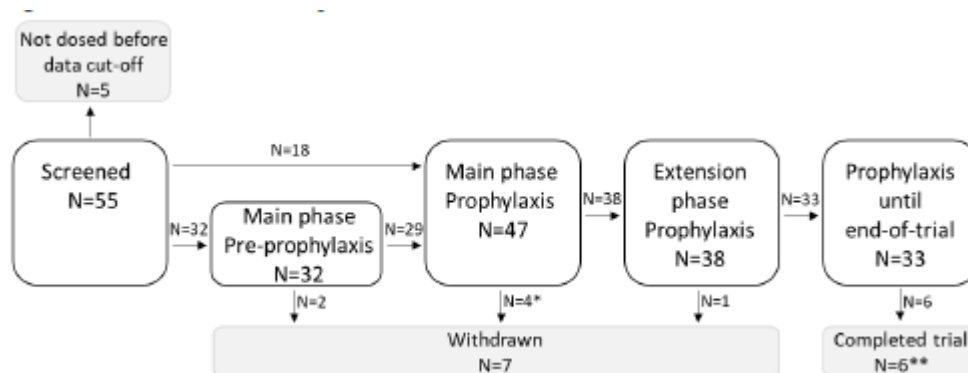


Figure 11: Patient flow

Main phase was completed when the patient had achieved 50 exposure days in trial at visit 23. Extension phase was completed when the patient had achieved 100 exposure days in trial at visit 28. Numbers in boxes describe the number of patients within each phase. Numbers between boxes describe the patient flow within the trial. *One patient withdrew after completion of the main phase and before entering the extension phase. **One patient discontinued treatment after completion of the extension phase and counted as completer of the trial.

Table 20: Patient disposition

	Pre-prophylaxis	Prophylaxis	Total
Screened	-	-	55
Treatment at the start of trial	32	18	50
Patients switching from pre-prophylaxis to prophylaxis	29	-	-
Exposed*, N(%)	32 (100.0)	47 (100.0)	50 (100.0)
Completed main phase, N(%)	- (-)	39 (83.0)	39 (78.0)
Withdrawal during main phase**, N(%)	2 (6.3)	4 (8.5)	6 (12.0)
Adverse event	2 (6.3)	3 (6.4)	5 (10.0)
Withdrawal by parent/guardian	0 (0.0)	1 (2.1)	1 (2.0)
Entered extension phase, N(%)	- (-)	38 (80.9)	38 (76.0)
Completed extension phase, N(%)	- (-)	33 (70.2)	33 (66.0)
Withdrawal during extension phase, N(%)	- (-)	1 (2.1)	1 (2.0)
Withdrawal by parent/guardian	- (-)	1 (2.1)	1 (2.0)
Completed trial, N(%)	- (-)	6 (12.8)	6 (12.0)
Full analysis set*, N(%)	32 (100.0)	47 (100.0)	50 (100.0)
Safety analysis set*, N(%)	32 (100.0)	47 (100.0)	50 (100.0)
Undergone minor surgery, N(%)	5 (15.6)	18 (38.3)	21 (42.0)
Undergone major surgery, N(%)	- (-)	1 (2.1)	1 (2.0)
Years in trial**	22.1	120.1	142.3
EDs in trial*	346	6363	6709

ED: exposure days.

*Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns.

**Includes patients withdrawn after main phase before entering extension phase.

+ Years in trial: Sum of years in trial for all patients (for discontinued patients time from discontinuation of treatment to end of trial is excluded).

Note that one patient can have multiple surgeries.

The full analysis set and the safety analysis set both consist of all patients exposed to nonacog beta pegol.

Cross-reference: R0T Table 14.2.1

The FAS and SAS included all 50 patients exposed to nonacog beta pegol. Five (5) patients did not initiate dosing before the interim cut-off date (25 November 2020) and, thus, were excluded from the FAS and SAS. A total of 32 patients in the age range of 0–1 years started on pre-prophylaxis treatment, and 18 patients started directly on prophylaxis treatment. A total of 29 patients switched from pre-prophylaxis to prophylaxis treatment. For the 47 patients on prophylaxis regimen period, the age range at entry was 0–5 years. A total of 21 patients underwent minor surgeries, and 1 patient

underwent major surgery during the trial. Overall, 7 patients were withdrawn from the trial, of which 5 withdrawals were due to AEs. Of the patient withdrawn due to AEs, 2 patients were on pre-prophylaxis treatment, 2 patients were in the main phase on prophylaxis treatment and 1 patient was withdrawn after completing the main phase and before entering the extension phase. Two (2) patients were withdrawn by their parents/LAR(s), of whom 1 was withdrawn during main phase after 32 EDs and 1 was during the extension phase after 60 EDs.

Table 21: Withdrawn patients

Full analysis set flag	Discontinuation date	Discontinuation term	Discontinuation event	Withdrawal criteria*	Withdrawal from the trial
Yes	21DEC2016	Adverse Event	Other		Yes
Yes	28DEC2017	Adverse Event	Development of FIX inhibitors > 5 BU confirmed by two consecutive tests	W2	Yes
Yes	29MAY2019	Adverse Event	Other		Yes
Yes	31OCT2019	Withdrawal By Parent/Guardian	Parental decision to initiate itti 'with another fix product'		Yes
Yes	27FEB2019	Withdrawal By Parent/Guardian	Withdrawal by parents		Yes
Yes	04JUN2019	Adverse Event			No**
Yes	05JUN2019	Adverse Event	Other		Yes
Yes	31DEC2014	Adverse Event	Anaphylactic reaction to the trial product	W3	Yes

*Number refers to the withdrawal criteria in the protocol.

** One patient discontinued treatment after completing the extension phase.

Recruitment

No screening failures occurred in this trial.

Conduct of the study

Changes in planned analyses

According to the trial protocol, the prophylactic effect was to be evaluated and presented for data from the main phase, extension phase and combined. However, as the patients stayed on the same treatment throughout both the main phase and the extension phase, there was no reason to evaluate the main and extension phase separately. Therefore, the evaluation of the prophylactic effect was based on data available up until the cut-off date. However, for comparison, estimated ABRs and haemostatic effects were presented as combined as well as separate for prophylaxis main phase and extension phase.

Additional analysis of the estimated mean steady state FIX trough levels was made 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. Plasma concentrations below LLOQ were set to half the value of the LLOQ.

To analyse the trajectories of neurological examinations over time, shift plots were added by examining the proportion of neurological examination items which shifted between every two

consecutive examinations. For each item, the shifts were categorised into one of the three following groups:

- Shift up (improved): from abnormal to normal findings
- Shift down (worsening): from normal to abnormal findings
- No change: from abnormal to abnormal; or from normal to normal findings

To analyse the trajectories of neurocognitive assessments over time, the following outputs of z-scores (against eTHINK) were added/adjusted in addition to the pre-specified individual plots:

- Summary tables of z-scores/change from prior assessment/change from initial assessment by assessment as well in total, which replaced the pre-specified summary table by visit as the neurocognitive assessments were performed at very different visits leading to sparse data by visit;
- Heat maps of mean value of change in z-scores at each subsequent assessment from initial assessment;
- Random regression model of z-scores, with exposure day as fixed effect and subject as random effect, allowing random intercept and random slope for exposure day for each individual subject. Due to limited amount of neurocognitive data at this interim, the random regression model was only performed for executive function domain and attention/processing speed domain which were collected for all countries.

The initial and subsequent categorical evaluations (clinical concern and contributing factor) from the EERP meetings were listed, together with corresponding exposure days (EDs).

For the preparation of EERP summary report, additional statistical outputs (summary tables and listing of Clinical Concern/Contributing Factor; statistical analyses of Clinical Concern by patient demographics/z-scores; statistical analyses of Clinical Concern/Contributing factor by SDH/HH parameters; heat maps of z-scores; summary table and shift plots of neurological examinations) were provided per request from members of EERP.

No other changes to the planned statistical analyses were performed.

Protocol amendments

There were 6 amendments to the protocol in the main study. In the extension study, there were 2 further amendments (no. 7 and 8) to the protocol at the time of the cut-off date (25 November 2020). All protocol amendments were approved according to local requirements prior to implementation and are shown in the table below. None of the amendments issued after the first visit were considered to have any influence on the interpretation of the results from the trial.

Table 22: Amendments of the protocol

Amendment number	Issue date	Timing of change	Countries affected	Key changes (for changes issued after FPFV)
1	25 March 2015	After FPFV	Global	This amendment allowed major surgery, specified requirements for major surgery and the data items to be recorded, ensured that genotyping of the haemophilia B mutation was collected, and minor clarifications and corrections to protocol version 1.0.
2	15 January 2016	After FPFV	Israel	This amendment allowed to take permission for obtaining the FIX genotype of withdrawn patient, if already available.
3	03 October 2016	After FPFV	Global	This amendment was retracted after release for submission as the described colour of the reconstituted trial drug was not in alignment with Q-IMPD.
4	13 December 2016	After FPFV	Global	This amendment specified the change in the colour of the reconstituted solution from "clear and colourless to slightly yellow solution" to "clear and colourless solution free from clearly visible particles".
5	11 December 2017	After FPFV	Global	This amendment included following parameters: neurological examination, biochemistry analysis, PEG analysis and height to certain visits. Patient participation in the trial was also clarified. It was also specified that all CNS related AEs were to be categorised as MESI.
6	29 June 2018	After FPFV	Global	This amendment included neurocognitive assessments* and specified that all renal AEs were to be categorised as MESI.
7	31 July 2019	After FPFV	Spain	This amendment allowed patients to discontinue treatment temporarily or permanently without need for withdrawal from the trial.
8	05 November 2019	After FPFV	Global	This amendment extended the recruitment period to increase the number of patients on trial product to increase the number of baseline neurocognitive assessments collected in the trial.

*Data from this amendment were not available at the cut-off date for the former iCTR reported on 29 March 2019.

Protocol deviations

PDs were categorised as important or non-important. Important PDs were deviations that could significantly impact the completeness, accuracy and/or reliability of the trial data or that could significantly affect the subject's rights, safety or well-being. In total, 267 important PDs were reported in this trial, of which 6 were at trial level, 2 were at country level, 32 were at trial site level, and 227 were patient level PDs. In addition, 10 patient level PDs that occurred before the interim data cut-off date (25 November 2020) were closed. None of the PDs were considered to have an overall impact on the trial conduct, subject safety or data interpretation.

In 2018, Novo Nordisk started following Drug Information Association (DIA) categorisation for reporting of PDs. In this trial, PDs reported before 01 January 2019 were categorised according to Novo Nordisk PD categorisation and PDs reported after 01 January 2019 were categorised according to DIA PD categorisation. This iCTR includes all PDs categorised per these two categorisation methods.

Table 23: Summary of important protocol deviations at trial and patient site

Protocol deviation category	Site level (count of protocol deviations)	Patient level (count of protocol deviations)
Drug Information Association (DIA) categories		
Informed consent	-	5
Inclusion/exclusion criteria	-	-
Treatment administration	2	18
Trial procedures/assessment	7	25
Concomitant medication	-	1
Subject visit schedule	-	3
SAE notification/safety procedure	1	5
Novo Nordisk categories		
Informed consent	1	15
Incl./excl./rand. criteria	-	2
Treatment compliance	2	99
Assessment deviations (incl. lab)	2	15
Trial product handling	5	19
Other	12	20
Total	32	227

Cross-reference: [Appendix 16.2.2.Listings 16.2.2.5 and 16.2.2.7](#)

Baseline data

Table 24: Baseline demographics – full analysis set

	Pre-prophylaxis	Prophylaxis	Total
Number of patients	32	47	50
Age at baseline (years)			
N	32	47	50
Mean (SD)	0.3 (0.5)	0.9 (1.1)	0.8 (1.1)
Median	0.0	1.0	1.0
Min ; Max	0 ; 1	0 ; 5	0 ; 5
Body weight (kg)			
N	32	47	50
Mean (SD)	8.9 (2.3)	10.4 (3.3)	10.3 (3.2)
Median	9.1	10.0	9.9
Min ; Max	3.0 ; 13.6	3.0 ; 22.2	3.0 ; 22.2
Height (cm)			
N	31	47	49
Mean (SD)	71.2 (8.9)	77.5 (12.9)	77.3 (12.7)
Median	73.2	76.0	76.0
Min ; Max	47.0 ; 86.0	47.0 ; 119.0	47.0 ; 119.0
Ethnicity, N(%)			
N	32 (100.0)	47 (100.0)	50 (100.0)
Not Hispanic or Latino	32 (100.0)	45 (95.7)	48 (96.0)
Hispanic or Latino	-	2 (4.3)	2 (4.0)
Race, N(%)			
N	32 (100.0)	47 (100.0)	50 (100.0)
Asian	9 (28.1)	17 (36.2)	17 (34.0)
Black or African American	6 (18.8)	5 (10.6)	6 (12.0)
White	14 (43.8)	22 (46.8)	24 (48.0)
Other	3 (9.4)	3 (6.4)	3 (6.0)

SD: standard deviation.

Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns.

The baseline value for height is the measurement at screening visit 0. If the visit 1 was more than a month after visit 0, the height was to be redone at visit 1; in such a case the value from visit 1 was used as baseline.

Haemophilia history at baseline

The haemophilia bleed and treatment history of patients are summarised in the table 25 and included PUPs, or patients with a history of less than 3 EDs on other FIX products, with no history of inhibitors. All 50 patients were males with severe or moderate haemophilia B with numeric FIX levels available from the medical history of 22 patients.

There were 2 patients with high ($\geq 2\%$) FIX levels prior to N9-GP exposure. One (1) patient had another commercial FIX product before screening (on the day before the baseline FIX levels were measured) and for the other patient mixing of blood samples during screening was suspected. New samples were taken to confirm FIX activity and both these patients reported $\leq 2\%$ FIX levels. These patients met the inclusion criteria later and were included in the trial. Overall, 56.0% (N=28) of patients had no relatives with recorded haemophilia B. One patient had a relative with history of inhibitors (shown in the table below).

Table 25: Haemophilia history – full analysis set

	Pre-prophylaxis	Prophylaxis	Total
Number of patients	32	47	50
FIX level (%) from medical history			
N	14	22	22
Mean (SD)	0.7 (0.4)	0.9 (0.7)	0.9 (0.7)
Median	0.9	1.0	1.0
Min ; Max	0.0 ; 1.0	0.0 ; 3.6	0.0 ; 3.6
FIX level (%) from medical history in ranges, N(%)			
N	18 (100.0)	25 (100.0)	28 (100.0)
<0.5	-	1 (4.0)	1 (3.6)
<1.0	17 (94.4)	23 (92.0)	25 (89.3)
<2.0	1 (5.6)	1 (4.0)	2 (7.1)
FIX level (%) at screening*			
N	23	38	41
Mean (SD)	0.8 (1.6)	1.0 (1.7)	1.0 (1.7)
Median	0.5	0.5	0.5
Min ; Max	0.5 ; 8.2	0.5 ; 8.2	0.5 ; 8.2
History of haemophilia B among relatives, N(%)			
N	32 (100.0)	47 (100.0)	50 (100.0)
Yes	15 (46.9)	19 (40.4)	21 (42.0)
No	17 (53.1)	27 (57.4)	28 (56.0)
Unknown	-	1 (2.1)	1 (2.0)
Relatives with haemophilia B**, N(%)			
N	15 (100.0)	19 (100.0)	21 (100.0)
Siblings / Cousins	5 (33.3)	5 (26.3)	6 (28.6)
Siblings / Cousins / Maternal Uncle / Other	-	1 (5.3)	1 (4.8)
Siblings / Cousins / Other	2 (13.3)	2 (10.5)	2 (9.5)
Maternal Uncle	1 (6.7)	2 (10.5)	2 (9.5)
Maternal Grandfather	2 (13.3)	3 (15.8)	3 (14.3)
Maternal Grandparents Brothers	1 (6.7)	1 (5.3)	1 (4.8)
Maternal Uncle / Other	1 (6.7)	2 (10.5)	2 (9.5)
Maternal Grandfather / Maternal Grandparents Brothers / Other	1 (6.7)	1 (5.3)	1 (4.8)
Other	2 (13.3)	2 (10.5)	3 (14.3)
Relatives with inhibitors**, N(%)			
N	1 (100.0)	1 (100.0)	1 (100.0)
Other	1 (100.0)	1 (100.0)	1 (100.0)

SD: standard deviation.

Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns.

* Plasma activities below lower limit of quantification (LLOQ) are set to half of LLOQ.

** N refers to the number patients with answer 'Yes' to the question.

Numbers analysed

Trial patients: Trial 3895 enrolled 55 male PUPs with haemophilia B and FIX activity $\leq 2\%$. As of the interim cut-off date (25-Nov-2020), 50 patients were exposed to nonacog beta pegol for a total of 6709 EDs, and the corresponding mean (SD) ED per patient was 134.2 (92.8) EDs. The cumulative exposure time in the trial was 142.3 years, and the corresponding mean (range) exposure period per patient was 2.85 (0.17–6.11) years. Patients' median age was 1 year (range: 0–5 years). Of the 50 patients, 39 completed the main phase (pre-prophylaxis and prophylaxis) and 33 completed the extension phase (prophylaxis only). Of the 33 patients who completed the extension phase, 6 patients have completed the trial while 27 patients currently remain in the prophylaxis period until end of trial (30-Oct-2022).

Outcomes and estimation

Annualised bleeding rate (ABR)

The median ABR for patients on prophylaxis treatment was 0.25 bleeds/patient/year and the total mean estimated ABR based on the negative binomial regression model was 0.94 [0.55; 1.61] bleeds/patient/year. When focusing on the estimated ABR over time, including patients on prophylaxis treatment in the main phase and extension phase, these were 1.02 [0.47; 2.19]_{95% CI} and 0.67 [0.40; 1.14]_{95% CI} bleeds/patient/year, respectively. A summary of the estimated ABR is presented in the Table below.

Table 26: Annualised bleeding rate - FAS

	Pre-prophylaxis	Prophylaxis	Total
Number of patients	32	47	50
Number of patients with bleeds, N(%)	22 (68.8)	25 (53.2)	35 (70.0)
Number of patients with 0 bleeds, N(%)	10 (31.3)	22 (46.8)	15 (30.0)
Number of bleeds	70	78	148
Bleeds per patient (min ; max)	0 ; 16	0 ; 14	0 ; 20
Mean treatment period (years)	0.69	2.56	2.85
Individual ABRs			
N	32	47	50
Mean (SD)	2.84 (3.57)	1.34 (3.41)	1.44 (2.59)
Median	1.46	0.25	0.51
Interquartile range	0.00 ; 4.61	0.00 ; 1.07	0.00 ; 1.18
Min ; Max	0.00 ; 16.23	0.00 ; 17.39	0.00 ; 13.25
Negative binomial estimate of ABR	-	0.94	-
95% CI	-	0.55 ; 1.61	-
Poisson estimate of ABR	-	0.65	-
95% CI	-	0.34 ; 1.25	-
LOCF sensitivity analysis			
Number of patients with less than 30 days of exposure	-	1	-
Number of patients with LOCF*	-	3	-
Bleeds per patient (min ; max)	-	0 ; 14	-
Mean treatment period (years)	-	2.60	-
Negative binomial estimate of ABR	-	0.85	-
95% CI	-	0.51 ; 1.41	-
Poisson estimate of ABR	-	0.64	-
95% CI	-	0.34 ; 1.18	-

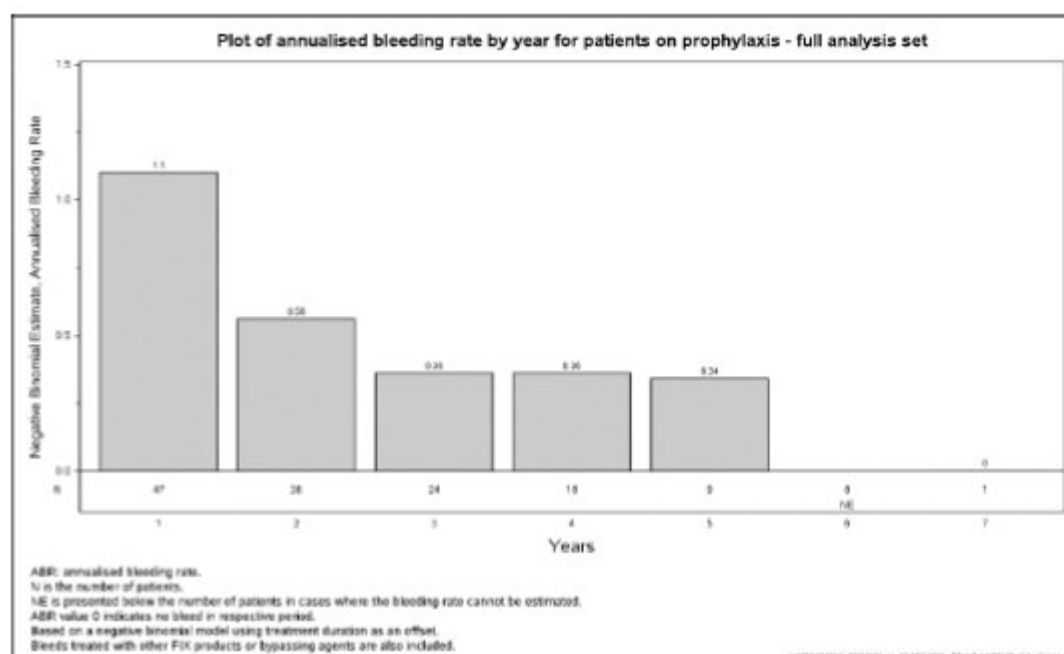
ABR: annualised bleeding rate, SD: standard deviation, CI: confidence interval, LOCF: last observation carried forward.
 Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns.
 Based on a negative binomial model using treatment duration as an offset.
 A sensitivity analysis was carried out using the poisson regression model allowing over-dispersion and using treatment duration as an offset.
 Bleeds treated with other FIX products or bypassing agents are also included.
 * Number of withdrawals with at least 1 month of treatment.
 nn7999-3895/ctr_20210521_er - 02-SEP-2021 - tabr/t_14200070_abr.txt

Table 27: Annualised bleeding rate by study phase - FAS

	Main phase prophylaxis	Extension phase prophylaxis	Prophylaxis throughout trial ¹
Number of patients	47	38	47
Number of patients with bleeds, N(%)	13 (27.7)	18 (47.4)	25 (53.2)
Number of patients with 0 bleeds, N(%)	34 (72.3)	20 (52.6)	22 (46.8)
Number of bleeds	29	49	78
Bleeds per patient (min ; max)	0 ; 10	0 ; 5	0 ; 14
Mean treatment period (years)	0.75	2.23	2.56
Individual ABRs			
N	47	38	47
Mean (SD)	1.29 (3.63)	0.74 (1.47)	1.34 (3.41)
Median	0.00	0.00	0.25
Interquartile range	0.00 ; 1.02	0.00 ; 0.88	0.00 ; 1.07
Min ; Max	0.00 ; 17.39	0.00 ; 8.03	0.00 ; 17.39
Negative binomial estimate of ABR	1.02	0.67	0.94
95% CI	0.47 ; 2.19	0.40 ; 1.14	0.55 ; 1.61

ABR: annualised bleeding rate, SD: standard deviation, CI: confidence interval
 Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns.
 Based on a negative binomial model using treatment duration as an offset.
 Bleeds treated with other FIX products or bypassing agents are also included.
 Time since last dose is only calculated if complete timepoints are available.
¹ Prophylaxis treatment during main phase, extension phase and prophylaxis until end of trial.

Cross reference: Modified from EOT Table 14.2.9, 14.2.10 and 14.2.11.

**Figure 12: Annualised bleeding rate by year for patients on prophylaxis - FAS**

Target joints

For patients on prophylaxis treatment, the estimated joint ABR was 0.11 [0.06; 0.20]95% CI bleeds/patient/year. None of the patients included in this trial fulfilled the criteria of target joint bleeds.

Haemostatic effect

Table 28: Haemostatic response - FAS

	Pre-prophylaxis	Prophylaxis	Total
Number of patients	32	47	50
Number of patients with bleeds, N(%)	21 (65.6)	24 (51.1)	34 (68.0)
Number of patients with 0 bleeds, N(%)	11 (34.4)	23 (48.9)	16 (32.0)
Number of bleeds	63	77	140
Haemostatic response, N(%)			
N	63 (100.0)	77 (100.0)	140 (100.0)
Excellent	44 (69.8)	44 (57.1)	88 (62.9)
Good	17 (27.0)	30 (39.0)	47 (33.6)
Moderate	2 (3.2)	3 (3.9)	5 (3.6)
Poor	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Success/failure, N(%)			
N	63 (100.0)	77 (100.0)	140 (100.0)
Success	61 (96.8)	74 (96.1)	135 (96.4)
Failure	2 (3.2)	3 (3.9)	5 (3.6)
Success/failure (incl. missing as failure), N(%)			
N	63 (100.0)	77 (100.0)	140 (100.0)
Success	61 (96.8)	74 (96.1)	135 (96.4)
Failure	2 (3.2)	3 (3.9)	5 (3.6)

Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns. Only bleeds treated with nonacog beta pegol and no other FIX products or bypassing agents are included.

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

nn7999-3895/ctr_20210521_er - 02-SEP-2021 - thr/t_14200209_haem.txt

Table 29: Details on five patients with treatment failures

Treatment regimen	Location of bleed	Severity of bleed	Time from start of bleed until first administration of nonacog beta pegol, hours	Number of injections to treat bleed
Pre-prophylaxis	Muscular	Severe	38.5	2
Pre-prophylaxis	Joint	Mild/ Moderate	39.9	1
Prophylaxis	Skin	Mild/ Moderate	NA	2
Prophylaxis	Skin	Mild/ Moderate	2.3	2
Prophylaxis	Skin	Mild/ Moderate	3.2	14

Nonacog beta pegol consumption

Table 30: Actual consumption of nonacog beta pegol - FAS

	Pre-prophylaxis	Prophylaxis	Total
Number of patients	32	47	50
Consumption used for treatment* per year per patient** (IU/kg/year)			
N	32	47	50
Mean (SD)	913.0 (1016.1)	2337.6 (473.0)	1991.7 (762.2)
Median	765.6	2312.2	2096.4
Min / Max	53.2 / 5895.0	242.7 / 4554.5	111.5 / 5433.5
Average prophylaxis dose*** (IU/kg)			
N	0	6253	6253
Mean (SD)	- (-)	43.6 (3.1)	43.6 (3.1)
Median	-	44.1	44.1
Min / Max	- / -	10.2 / 54.0	10.2 / 54.0
Average pre-prophylaxis dose*** (IU/kg)			
N	241	0	241
Mean (SD)	40.7 (5.1)	- (-)	40.7 (5.1)
Median	40.7	-	40.7
Min / Max	6.1 / 53.0	- / -	6.1 / 53.0
Average dose for minor surgery*** (IU/kg)			
N	5	29	34
Mean (SD)	64.4 (21.6)	61.2 (19.5)	61.7 (19.5)
Median	79.1	46.5	61.5
Min / Max	38.6 / 80.6	37.5 / 89.3	37.5 / 89.3
Average dose for major surgery*** (IU/kg)			
N	0	2	2
Mean (SD)	- (-)	45.6 (0.0)	45.6 (0.0)
Median	-	45.6	45.6
Min / Max	- / -	45.6 / 45.6	45.6 / 45.6
Average dose for treatment of bleed+ (IU/kg/bleed)			
N	63	77	140
Mean (SD)	47.7 (17.6)	58.5 (70.0)	53.7 (53.3)
Median	41.2	44.2	43.3
Min / Max	36.1 / 130.4	27.8 / 636.1	27.8 / 636.1
Number of days between doses****+			
N	0	6206	6206
Mean (SD)	- (-)	7.0 (1.1)	7.0 (1.1)
Median	-	7.0	7.0
Min / Max	- / -	0.0 / 35.0	0.0 / 35.0
Frequency of doses in/out of compliance*****, N(%)			
N	-	6206 (100.0)	6206 (100.0)
6-8 days	-	5963 (96.1)	5963 (96.1)
<6 days	-	114 (1.8)	114 (1.8)
>8 days	-	129 (2.1)	129 (2.1)

SD: standard deviation.

Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns.

* Consumption used for treatment includes all doses given.

** N is the number of patients.

*** N is the number of doses.

+ N is the number of bleeds. Only bleeds treated with nonacog beta pegol and no other FIX products or bypassing agents are included.

++ 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

Summary of main studies

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

Table 31: Summary of Efficacy for trial 3774

Title: Safety, Efficacy and Pharmacokinetics of NNC-0156-0000-0009 (nonacog beta pegol) in Previously Treated Children with Haemophilia B - Results of the main and extension phases			
Study identifier	NN7999-3774		
Design	An open-label, single-arm, multinational, non-controlled trial investigating safety, efficacy and pharmacokinetics of NNC-0156-0000-0009 (nonacog beta pegol) in prophylaxis and treatment of breakthrough bleeds in previously treated children with haemophilia B (12 years of age and younger at inclusion)		
	Duration of main phase:	16 May 2012 until 07 April 2014	
	Duration of Extension phase:	Until 25 November 2020 (interim cut-off date for clinical database) - ongoing	
Hypothesis	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		
Treatments groups	Prophylaxis	40 IU/Kg once weekly, 25 patients (12 were 0-6 years and 13 were 7- 12 years at study enrolment)	
Endpoints and definitions	Primary endpoint	Safety	Incidence of inhibitory antibodies against FIX defined as titre ≥ 0.6 BU
	Secondary endpoint	Safety	Adverse events including serious adverse events (SAEs) and medical events of special interest (MESI), and development of host cell protein (HCP) antibodies
	Secondary endpoint	Efficacy and PK	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: Incremental recovery at 30 minutes, Trough level (single-dose and steady state), Area under curve, terminal half-life, clearance, mean residence time, volume of distribution at steady state, FIX activity at 30 minutes (single dose and steady state)
Database lock	25 November 2020 (interim cut-off date for clinical database) 08 February 2021 (interim database lock and cut-off date for Argus safety database)		

Results and Analysis				
Analysis description	Efficacy Analysis			
Analysis population and time point description	Full analysis set (FAS) – all patients with efficacy data after exposure to nonacog beta pegol. The analysis of efficacy and PK data was based on FAS. Data refer to main and extension phase.			
Descriptive statistics and estimate variability	Age group	0-6 years	7-12 years*	All**
	Number of subject	12	23	25
	Poisson estimate of ABR (95%CI)	1.02 (0.68; 1.54)	0.84 (0.41; 1.75)	0.85 (0.51; 1.40)
	Haemostatic response in treatment of bleeds	88% treatment success	93% treatment success	89.1% treatment success
	Consumption (IU/kg/year) – Mean (SD); Median (min; max)	2208.6 (78.9); 2223.1 (2015.1; 2312.3)	2324.8 (83.3); 2322.9 (2120.6; 2466.8)	2270.4 (111.3); 2277.8 (2015.1; 2512.4)
	Prophylaxis dose (IU/kg) – Mean (SD); Median (min; max)	42 (1.6); 41.9 (14.3; 56)	43.7 (1.8); 44 (6.4; 49.6)	43.2 (1.7); 43.2 (6.4; 56)
	Number of injections needed to treat bleed	1 – 82.9% 2 – 14.3% 5 – 2.9%	1 – 84.1% 2 – 12.7% 3 – 3.2%	1 – 82% 2 – 11.7% 3 – 3.1% 5 – 0.8% 7 – 1.6% 12 – 0.8%
	Dose for treatment of bleed from start to stop (IU/kg/bleed) – Mean (SD); Median (min; max)	53.6 (32.2); 42.2 (21.9; 213.4)	50.6 (20.4); 43.2 (26.7; 136)	60 (60.4); 43.1 (21.9; 569.3)

* Note that several subjects crossed age groups during trial conduct, n=10 contributed to both paediatric age categories

** All refers to all subjects included in the trial independent whether age groups were crossed, note that n=15 patients became >12 years during the trial

Table 32: Summary of Efficacy for trial 3895

Title: Safety and Efficacy of NNC-0156-0000-0009 (Nonacog beta pegol) in Previously Untreated Patients with Haemophilia B - Results from the Main and Extension Phases			
Study identifier	NN7999-3895code		
Design	An open-label single-arm multicentre non-controlled phase 3a trial investigating safety and efficacy of nonacog beta pegol (N9-GP) in prophylaxis and treatment of bleeding episodes in previously untreated patients with haemophilia B (FIX activity ≤2%)		
	Duration of main phase:	02 July 2014 (first patient first visit) until 31 August 2018	
	Duration of Extension phase:	Until 25 November 2020 (data cut-off date) - ongoing	
Hypothesis	Primary Objective: - To evaluate immunogenicity of N9-GP (nonacog beta pegol) Secondary Objectives: - To evaluate safety of N9-GP (nonacog beta pegol) - To evaluate efficacy of N9-GP (nonacog beta pegol) • in long-term prophylaxis treatment • in the treatment of bleeding episodes • through the surrogate marker: FIX activity • through monitoring of number of doses and consumption of N9-GP		
Treatments groups	Pre-prophylaxis		On-demand treatment of bleeding episodes with 40 IU/kg N9-GP (or 80 IU/kg for a severe bleed) - until 24 months of age or until 20 ED, 32 PUPs
	Prophylaxis		40 IU/Kg once weekly, in total 47 PUPs during the trial (n=29 switched from pre-prophylaxis)
Endpoints and definitions	Primary endpoint	Safety	Incidence of inhibitory antibodies against FIX
	Secondary endpoint	Safety	Number and frequency of adverse events, serious adverse events, and Medical Events of Special Interest
	Secondary endpoint	Efficacy and PK	Number of breakthrough bleeding episodes during prophylaxis (annualised bleeding rate) Haemostatic effect by 4-point haemostatic response scale ("excellent", "good", "moderate" and "poor") Incremental recovery at 30 minutes, FIX activity at 30 minutes and trough level Amount of drug administered and number of doses needed to treat a bleeding episode
Database lock	25 November 2020 (data cut-off date) 09 February 2021 (interim database lock and cut-off date for Argus safety database)		

Results and Analysis				
Analysis description	Efficacy Analysis			
Analysis population and time point description	Full analysis set (FAS) –Included all patients exposed to nonacog beta pegol. The efficacy analysis and descriptions will be based on the FAS. Data refer to main and extension phase.			
Descriptive statistics and estimate variability	Treatment group	Pre-prophylaxis	Prophylaxis	Total*
	Number of subject	32	47	50
	Poisson estimate of ABR (95%CI)	Not available	0.65 (0.34; 1.25)	Not available
	Negative binomial estimate of ABR (95%CI)	1.02 (0.47; 2.19)	0.67 (0.4; 1.14)	0.94 (0.55; 1.61)
	Haemostatic response in treatment of bleeds	96.8% treatment success	96.1% treatment success	96.4% treatment success
	Consumption (IU/kg/year) – Mean (SD); Median (min; max)	913 (1016.1); 765.6 (53.2; 5895)	2337.6 (473); 2312.2 (242.7; 4554.5)	1991.7 (762.2); 2096.4 (111.5; 5433.5)
	Pre-/Prophylaxis dose (IU/kg) – Mean (SD); Median (min; max)	40.7 (5.1); 40.7 (38.6; 80.6)	43.6 (3.1); 44.1 (10.2; 54)	
	Number of injections needed to treat bleed	1 – 90.2% 2 – 8.2% 3 – 1.6%	1 – 91.9% 2 – 6.8% 4 – 1.4%	1 – 91.1% 2 – 7.4% 3 – 0.7% 4 – 0.7%
	Dose for treatment of bleed from start to stop (IU/kg/bleed) – Mean (SD); Median (min; max)	47.7 (17.6); 41.2 (36.1; 130.4)	58.5 (70); 44.2 (27.8; 636.1)	53.7 (53.3); 43.3 (27.8; 636.1)

* Note that 29 PUPs switched from pre-prophylaxis to prophylaxis treatment during the trial

Analysis performed across trials (pooled analyses and meta-analysis)

An integrated summary of immunogenicity was submitted. The summary refers to completed trials 3639, 4260, 3747, 3773 and 3775 as well as ongoing trials 3774 and 3895. Immunogenicity data relevant for paediatric patients (i.e. from trials 3774 for PTPs and 3895 for PUPs) are discussed where relevant.

Supportive study

NN7999-4260

A multicentre, multinational, open-label, randomised, 2-sequence, 2-period cross-over trial comparing the single-dose PK of nonacog beta pegol and ALPROLIX, given as i.v. bolus injections to patients with haemophilia B with a FIX activity $\leq 2\%$ and without inhibitors, at a dose of 50 IU/kg for both products.

Treatment

- All patients received a single i.v. bolus injection of 50 IU/kg of nonacog beta pegol or ALPROLIX in a non-bleeding state

Number of dosed patients for PK assessment and sampling time points

- 15 patients (21-65 years) were exposed to a single dose of nonacog beta pegol and ALPROLIX during the trial
- PK was assessed at 2 sessions (Visits 2-9 and 10-17)
- Sampling time points (over 10 days): Pre-dose, 10min, 30min, 1h, 3h, 6h, 8h, 24h, 48h, 96h, 144h, 168h, 192h and 240h

Objectives and endpoints

- The primary objective was to compare the single-dose PK of nonacog beta pegol with ALPROLIX in patients with haemophilia B; this was assessed by the primary endpoint, which was based on the one-stage clotting assay:
 - Area under the FIX activity-time curve from 0 to infinity dose-normalised to 50 IU/kg ($AUC_{0-\infty, \text{norm}}$)
- The secondary objective was to compare the safety of nonacog beta pegol and ALPROLIX® in patients with haemophilia B. The secondary PK endpoints addressing this objective included:
 - Maximum FIX activity dose-normalised to 50 IU/kg ($C_{\text{max}, \text{norm}}$)
 - FIX activity 168 hours post dosing (C_{168h})
 - Incremental recovery 30 minutes post dosing (IR_{30min})
 - Terminal half-life ($t_{1/2}$)
 - Clearance (CL)

Pharmacokinetic assessments

The bioanalysis of FIX activity was performed by the central laboratory. The FIX activity was measured with 2 different bioassays that were developed for nonacog beta pegol and ALPROLIX in human plasma:

- FIX one-stage clotting assay
- FIX chromogenic assay

Normal human plasma (NHP) standard calibrated against the World Health Organisation (WHO) international FIX standard was used as an assay calibrator for all the assays. In addition, for the one-stage clotting assay for nonacog beta pegol, a product-specific standard (PSS) was also used. The FIX chromogenic assay for nonacog beta pegol and ALPROLIX and the one-stage clotting assay for ALPROLIX were qualified as fit for purpose. The FIX one-stage clotting assays for nonacog beta pegol

that used NHP and PSS calibration were validated according to bioanalytical guidelines. The activated partial thromboplastin time (aPTT) reagents and the FIX chromogenic assay kit used for the one-stage clotting assay and the chromogenic assay are specified in Table 33. Quality controlled FIX activity results were available and reviewed by Novo Nordisk A/S before database lock. A bioanalytical report (BAR) report was written for the assays.

Table 33: FIX activity assays for nonacog beta pegol and ALPROLIX

Investigational medicinal product	Assay	aPTT reagent/Kit	Calibrator
Nonacog beta pegol	one-stage clotting assay	SynthAFax®	normal human plasma
ALPROLIX®	one-stage clotting assay	Actin® FSL	normal human plasma
Nonacog beta pegol	one-stage clotting assay	SynthAFax®	product-specific standard
Nonacog beta pegol	chromogenic assay	Rox Factor IX	normal human plasma
ALPROLIX®	chromogenic assay	Rox Factor IX	normal human plasma

Abbreviations: aPTT = activated partial thromboplastin time.

FIX one-stage clotting assay

The FIX one-stage clotting assay measured the FIX activity of nonacog beta pegol and ALPROLIX by time to clot formation. This assay is based on the ability of the test sample to correct the aPTT-dependent clotting time of a plasma sample deficient in FIX but containing all other factors required for normal clotting. As FIX was a limiting factor, the clotting time was dependent on the FIX activity in the sample. The assay measured the time from initiation of the coagulation process until formation of the fibrin clot. The observed time to fibrin clot formation (turbidity measured as optical density) was inversely proportional to FIX activity.

FIX chromogenic assay

The FIX chromogenic assay is a two-stage activity assay and is based on the colour development by FXa cleavage of a chromogenic substrate. The plasma samples were incubated with coagulation factor XIa (FXIa), coagulation factor X (FX), coagulation factor VIII (FVIII), thrombin, phospholipids and calcium. This resulted in the activation of FIX (present in the plasma samples) to FIXa. The FIXa formed an enzymatic complex with thrombin-activated FVIII, phospholipids and calcium, thereby activating FX to FXa. The generated FXa then hydrolysed a chromogenic substrate and released p-nitroaniline, which was quantified by colorimetric detection. Thus, there was a direct relationship between the amount of FIXa in the plasma sample and the generated FXa.

Trial results

Table 34: AUC0-inf, norm for nonacog beta pegol and ALPROLIX – FAS

	NS-GP			ALPROLIX®	
	Chromogenic assay NHP	One-stage clotting assay PSS	One-stage clotting assay NHP+	Chromogenic assay NHP	One-stage clotting assay NHP++
Number of patients	14	14	14	14	14
AUC (0-inf) dose normalised (IU·h/mL)					
N	12	12	12	12	12
Mean (SD)	90.36 (14.46)	99.49 (15.17)	97.76 (15.63)	28.24 (6.88)	22.57 (5.71)
Median	91.40	97.40	97.28	27.95	22.29
Min ; Max	59.76 ; 109.6	76.77 ; 130.7	67.35 ; 123.7	19.35 ; 44.00	15.98 ; 35.32
CV %	17.40	15.11	16.72	23.52	23.66
Geometric Mean	89.20	98.46	96.56	27.54	21.99

NHP: Normal Human Plasma, PSS: Product-Specific, SD: Standard deviation, CV: Coefficient of Variation,
AUC: Area under the curve,
+ APTT reagent: SynthAFax®
++ APTT reagent: Actin® FSL

Table 35: mean FIX activity levels (IU/mL) at 10 minutes post-dose for nonacog beta pegol and APROLIX - FAS

	Nonacog beta pegol			ALPROLIX®	
	One-stage clotting assay NHP ^a	One-stage clotting PSS	Chromogenic assay NHP	One-stage clotting assay NHP ^b	Chromogenic assay NHP
Mean FIX activity (IU/mL)	0.911	0.908	0.789	0.464	0.579

^aaPTT reagent: SynthAFax®. ^baPTT reagent: Actin®FSL.

Abbreviations: aPTT = activated partial thromboplastin time; NHP = normal human standard; PSS = product-specific standard.

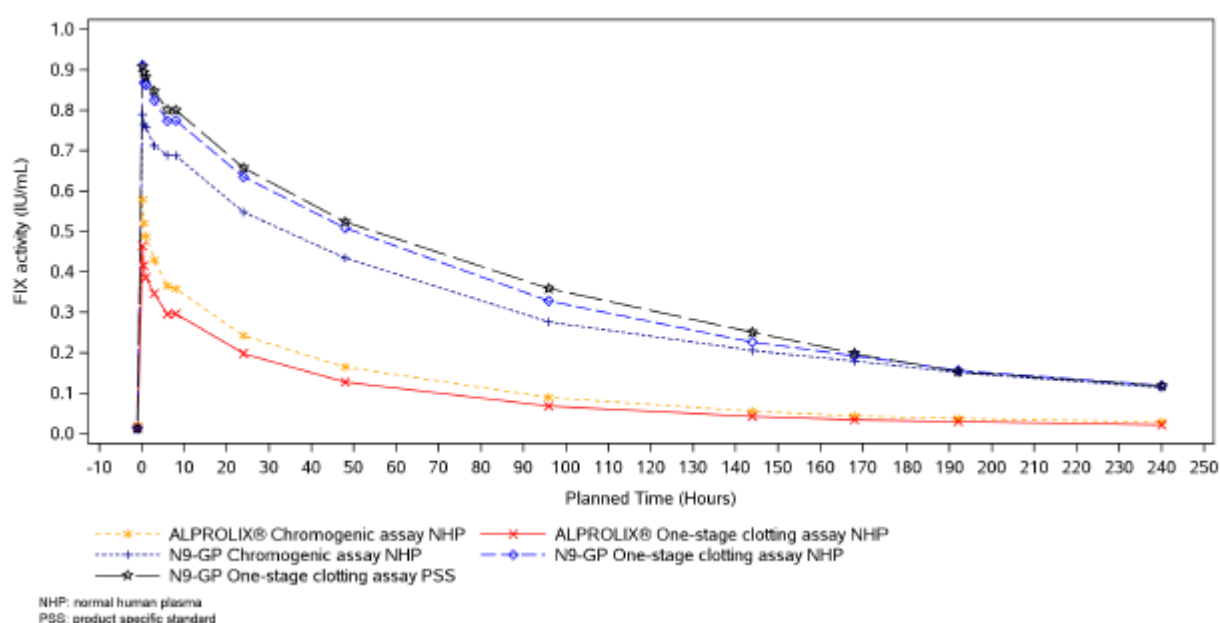


Figure 13: Mean profiles of Factor IX activity (IU/mL) for nonacog beta pegol and ALPROLIX - FAS

Estimated ratios of nonacog beta pegol/ALPROLIX along with 95%CI for the primary endpoint and the key secondary endpoints as measured with the one stage clotting assay (NHP) and the chromogenic assay (NHP) were:

AUC _{0-inf,norm} :	One stage clotting: 4.39 [4.06; 4.75]95%CI;	Chromogenic: 3.24 [2.94; 3.57]95%CI
C _{max,norm} :	One stage clotting: 2.02 [1.81; 2.25]95%CI;	Chromogenic: 1.43 [1.3; 1.57]95%CI
IR _{30min} :	One stage clotting: 2.20 [2.01; 2.40]95%CI;	Chromogenic: 1.56 [1.41; 1.73]95%CI
t _{1/2} :	One stage clotting: 1.22 [1.09; 1.35]95%CI;	Chromogenic: 1.35 [1.19; 1.54]95%CI
CL:	One stage clotting: 0.23 [0.21; 0.25]95%CI;	Chromogenic: 0.31 [0.28; 0.35] 95%CI

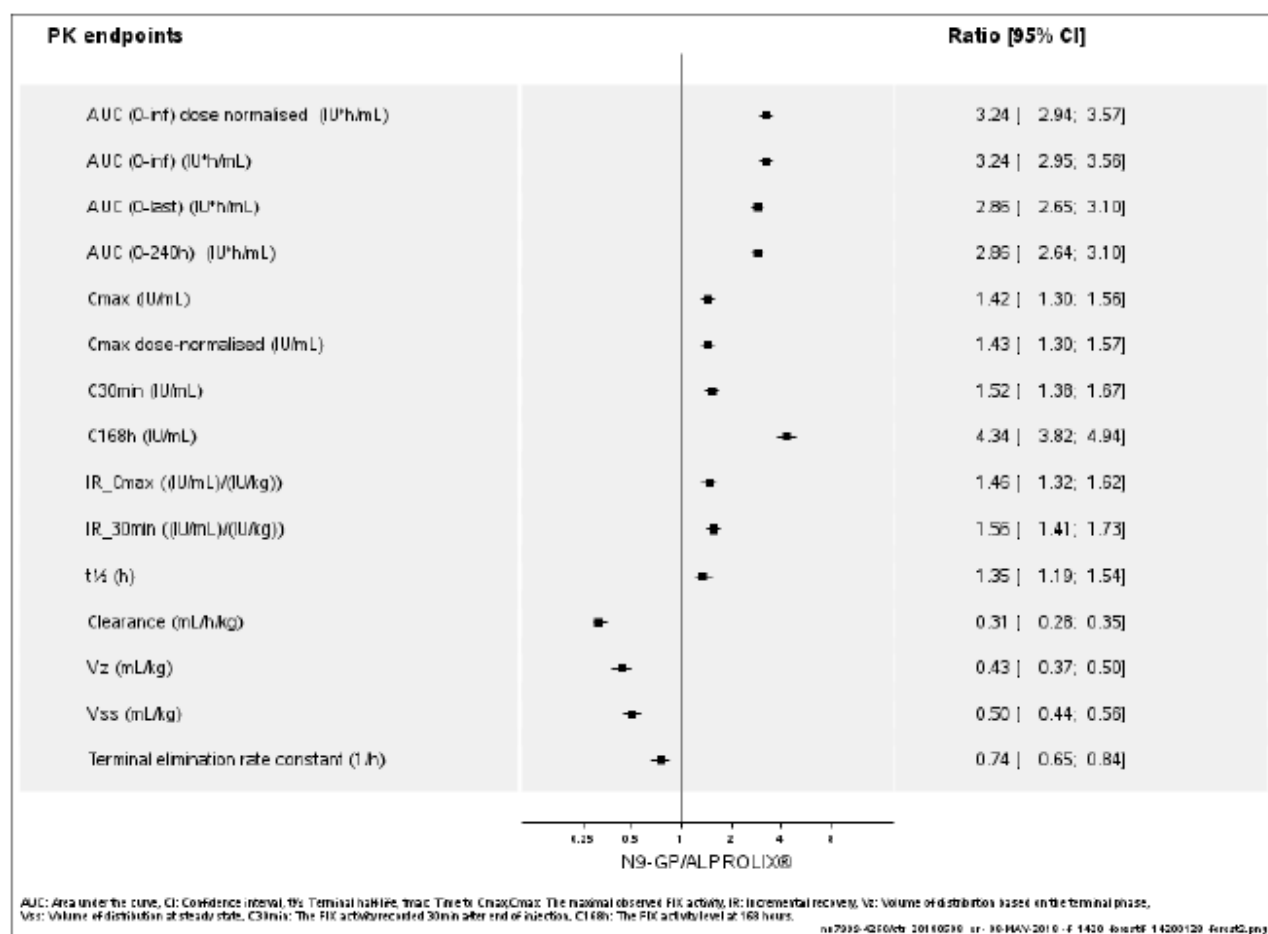


Figure 14: Forest plot of the PK endpoint – Chromogenic assay - FAS

2.4.2. Discussion on clinical efficacy

The MAH submitted long-term treatment data for two non-controlled, open-label paediatric studies; study 3774 followed 25 previously treated patients (PTPs) 0-12 years old (n=12 patients 0-6 years and n=13 patients 7-12 years old) and study 3985 followed 50 previously untreated patients (PUPs) 0-6 years old. The mean treatment period was >6 years for study 3774 and >2.5 years for study 3985.

Design and conduct of clinical studies

NN7999-3774

Data generated during the main phase of study 3774 (i.e. ≥52 weeks) were assessed during initial MAA in 2016. Long-term data generated during the extension phase (i.e. up to around 450 weeks) of this study are submitted for this variation. In total 22 subjects entered the extension study (n=11 patients 0-6 years and n=11 patients 7-12 years old) and 12 of these subjects remained in the study until the currently reported data cut. 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 none of the 10 subjects that 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=12 became 13-17 years old) and adult (n=3 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). Results are discussed by actual paediatric age groups that subjects belonged to while they were exposed and assessed for efficacy (i.e. n=12 younger children of 0-6 years and n=23 older children of 7-12 years with a total of n=25 subjects contributing to the dataset of both categories). It is noted that all subjects included in trial 3774 had severe (factor IX level $< 1\%$) or moderately severe (factor IX level $\leq 2\%$) 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 study plan, the mean (SD) prophylaxis dose during the study was 43.2 (1.7) IU/kg and 128 bleeds were treated with a median dose of 43.1 IU/kg/bleed (more details below). In total 8 protocol amendments and 306 important protocol deviations are reported until this latest data cut-off. Reported protocol amendments appear acceptable with respect to study conduct. The number of important protocol deviations appears very 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 it was concluded that none of the PDs (1 on country-level, 6 on trial level, 38 on trial site level and 261 on patient level) had an overall impact on the trial conduct, subject safety or data interpretation. It is further noted that PDs reported before 01 January 2019 were categorised according to Novo Nordisk PD categorisation and PDs reported after 01 January 2019 were categorised according to DIA PD categorisation. Importantly, the interim study report includes all PDs categorised per these two categorisation methods.

NN7999-3895

The MAH presents an open-label study to provide clinical evidence for PUPs with haemophilia B that were treated with Refixia following a pre-prophylactic (treatment of bleeds and/or reduced prophylaxis) and/or prophylactic (prevention of bleeds and treatment of bleeding episodes) regimen. A total of 55 previously untreated patients from 0-6 years were screened and 50 of these were dosed with nonacog beta pegol. Of the 50 exposed patients, 39 patients completed the main phase, 33 of these also completed the extension phase and 31 patients had been exposed to > 100 EDs. A total of 32 patients started on pre-prophylaxis treatment and a total of 47 patients were followed on prophylaxis treatment (29 of those switched from pre-prophylaxis to prophylaxis treatment during the trial). Overall, 7 patients were withdrawn from the trial of which 5 withdrawals were due to AEs and 2 withdrawals were due to parent withdrawal of consent. All withdrawn patients contributed with data until the date of withdrawal. The FAS and SAS consisted of 50 patients. Several of the subjects crossed age groups during the trial as they became older in the course of study conduct. However, all subjects remained in the paediatric category of ≤ 12 years. As per inclusion criteria ≤ 3 EDs to FIX containing products or 5 previous EDs to blood components were allowed for PUPs included in study 3985. In total 29 PUPs had previous exposure to FIX containing products and/or to blood components before enrolment. As per inclusion criteria all exposures to FIX products were limited to ≤ 3 EDs and all exposures to blood components were limited to ≤ 5 previous EDs. Around half of the subjects (n=15)

had previous exposure within one month prior screening. According to the GL on recombinant Factor IX products (EMA/CHMP/BPWP/144552/2009 rev. 2 Corr. 1) the formal clinical investigation in PUPs is formally not required for the licensure of paediatric patients. However, the study is endorsed. It is noted that all subjects included in trial 3895 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 severe bleeds and port implants (as part of the minor surgery) were planned to be treated with 80 IU/kg. In total 8 protocol amendments and 276 important protocol deviation are reported until this latest data cut-off. Reported protocol amendments appear acceptable with respect to study conduct. One of the protocol amendments was implemented, in order to allow major surgery during the trial, which appears acceptable. The number of important protocol deviations appears very high, but deviations are comparable to reported deviations in paediatric PTPs and in other Factor IX products. 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, all 50 patients exposed to nonacog beta pegol were included in the FAS as it was concluded that none of the PDs were considered to have an overall impact on the trial conduct, subject safety or data interpretation. It is further noted that PDs reported before 01 January 2019 were categorised according to Novo Nordisk PD categorisation and PDs reported after 01 January 2019 were categorised according to DIA PD categorisation. Importantly, the interim study report includes all PDs categorised per these two categorisation methods.

Efficacy data and additional analyses

NN7999-3774

Efficacy data in paediatric PTPs

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, as also assessed during initial MAA and presented in the EPAR for Refixia. 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.

Presented data from extension phase comprise all data until data cut-off (including those from main phase). Efficacy results appear principally in line with other Factor IX products with prolonged half-life that are licensed for paediatric subjects. The ABR after long term treatment was slightly reduced compared to the main phase for 0-6 years old (Poisson estimated ABR was 0.87 [95%CI: 0.38; 2.01] during the main study and 1.02 [95%CI: 0.68; 1.54] after study extension) and 7-12 years old (Poisson estimated ABR was 1.88 [95%CI: 1.14; 3.09] during the main study and 0.84 [95%CI: 0.41; 1.75] after study extension) PTPs. Comparable to the main phase most of the bleeds were traumatic bleeds after the extension phase (80% for 0-6 year old and 66.7% for 7-12 year old PTPs). The haemostatic success rate was around 90% in paediatric subjects (88.6% for 0-6 year old and 93.7% for 7-12 year old PTPs) and treatment failure was reported for 8 bleeds (4 per age group, from a total of 98 bleeds). All treatment failures occurred across muscular, mucosal, joint or subcutaneous locations, 6 were traumatic and 2 were spontaneous bleeds and all were mild/moderate bleeding

events. Poor treatment outcome is noted for two bleeds (both in one patient <6 years), all other failures were rated with moderate response. Only 2 bleeds in 2 subjects required >2 injections (3 and 5 injections, both traumatic bleeds).

It is highlighted that none of the breakthrough bleeding events in paediatric PTPs was rated as a severe bleeding event (all mild or moderate) and none of the patients was treated with other FIX products or bypassing agents. Furthermore, no new target joint developed throughout the whole observation period and the two pre-existing target joints had resolved during the main phase of the trial. One CNS bleed (extracranial) occurred throughout the study in a patient aged 0-6 years with an excellent haemostatic response.

The median prophylactic dose used (41.9 IU/kg for 0-6 year old subjects and 44 IU/kg for 7-12 year old subjects) as well as the median dose required to treat and stop bleeding events (42.2 IU/kg for 0-6 year old subjects and 43.2 IU/kg for 7-12 year old subjects) was 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 (82.9% and 84.1% of bleeds in 0-6 and 7-12 year old PTPs, respectively) and is in line with reported median doses during the main phase (see EPAR). In fact, only 3 of 98 bleeds required more than 2 injections (i.e. once 5 injections for one bleed in a subject ≤ 6 years were required and for two bleeds in a subjects ≤ 12 years 3 injections were required). The mean annual consumption of 2208.6 IU/kg for 0-6 year old and 2324.8 IU/kg for 7-12 year old patients is comparable to other Factor IX products with prolonged half-life. During main and extension phase the median duration of bleeds in the 0-6 years age group was 22.5 h (ranging from 0.2 to 666.3 h) and the median duration of bleeds in the 7-12 years age group was 24.5 h (ranging from 0.5 to 348.2 h). Median time from first dose to stop of bleed was 17.8 h (ranging from 0 to 665.5 h) and 13.5 h (ranging from 0 to 288.7 h). It is recognised that two of the reported bleeds were exceptionally long. One in the 0-6 year age group had a traumatic subcutaneous bleed (bruising around eye) over 666.3 hours that was treated with a total of 5 injections (40 IU/kg of nonacog beta pegol each) over a 7-day period. Another event of 119 hours in the 7-12 years age group was a mild, traumatic left elbow joint bleeding episode, the subject was treated twice for the bleeding episode (once for the initial bleed and once with prophylaxis).

The evaluation of PROs of treatment with N9-GP appear compromised by low patient numbers that contributed to these measures (0-3 years: 6 questionnaires; 4-7 years: 3 children and 4 parent questionnaires; 8-12 years: 8 questionnaires each, children and parents). Thus, 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.

After study protocol amendment 5 also major surgeries were allowed during the trial. A single major surgery in a 3 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, 17 minor surgeries were performed in 12 subjects ≤ 12 years with a mean dose level of 44.4 IU/kg. Upon request the MAH clarified that the additional prophylactic dose before surgery was administered in 10 of the 17 minor surgeries and in 7 cases no additional dose was administered besides the standard weekly prophylactic dose. The applied dose level was in line with the recommendation for preventive doses before minor surgeries. The haemostatic response to prophylactic treatment for minor surgeries was not recorded during study 3774.

No Factor IX inhibitors (≥ 0.6 BU) were detected in any of the patients of trial 3774. One patient developed transient anti-nonacog beta pegol antibodies during the trial (detected at visit 23 and 24, first after 324 EDs). Lack of cross-reactivity to rFIX indicated presence of anti-PEG antibodies at the first visit. Another patient developed anti-CHO HCP antibodies during trial 3774 (detected at visit 11 after 52 EDs). Importantly, no influence of antibodies on Factor IX activity was identified for that

patient and there were no clinical signs or symptoms reported. It is concluded that the immunogenic potential of nonacog beta pegol did not affect efficacy of the medication during the trial period in paediatric PTPs.

In summary, efficacy appears to be maintained over time in paediatric patients and dosing recommendations (i.e. once weekly dosing with 40 IU/kg) appear to suit the demand for the prophylactic treatment. None of the reported breakthrough bleeds was rated as a severe bleeding event. Still, the treatment of bleeds failed in 8 cases from a total of 98 bleeds, which requires further clarification, but does not indicate a major lack in efficacy for the treatment response to nonacog beta pegol in paediatric PTPs. Thus, also the treatment recommendation of 40 IU/kg for on demand mild/moderate bleeds can be followed in principle. It is concluded that reported efficacy results together with measured Factor IX activity at steady state (i.e. trough levels pre-dose) in the mild haemophilia range support the treatment of previously treated paediatric patients.

NN7999-3895

Efficacy data in paediatric PUPs

The evaluation of immunogenicity was the primary aim of study 3895. Efficacy in long-term prophylaxis treatment as well as the treatment of bleeding episodes 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 FIX products. The majority of the 148 bleeds during trial 3895 was reported as traumatic bleeds (73.6%) and mostly located in the skin (39.9% were traumatic skin bleeds). A re-bleed occurred in only one case and bleeds during prophylaxis occurred in a rather balanced manner ≤ 4 days (52.8%) and > 4 days (47.3%) after the last dose. The reported median duration of bleed is 20.6 hours, which is very comparable to the bleeding duration reported for PTPs ≤ 6 years (i.e. 20.3 hours). It is noted that 4.7% of all reported bleeds were considered severe bleeds (7.1% during pre-prophylaxis and 2.6% during prophylaxis treatment). In contrast, no severe bleeding events were reported for PTPs ≤ 6 years during trial 37774. Haemostatic outcomes are reported for 4 of the severe bleeding events (two excellent, one good and one moderate). The remaining 3 treated severe breakthrough bleeds (two traumatic and one spontaneous) were also treated with other FIX products or bypassing agents, which hampers interpretation of the response to nonacog beta pegol. From in total 8 bleeding episodes in 5 patients the use of other FIX products or bypassing agents is reported. Provided reasons (unavailability of trial product or lack of information regarding the clinical trial at the treating site, low titre inhibitors and one fatal CNS bleeding event treated with multiple agents in a subject considerably likely with positive FIX inhibitors) can be followed. In general, for the evaluation of haemostatic response only those events treated with nonacog beta pegol and no other FIX containing products or bypassing agents were considered. This is supported, as no clear treatment effect can be associated with nonacog beta pegol in these cases. Treatment failures were rare and all rated with moderate response (no reported poor treatment response), with one severe bleeding event (during pre-prophylaxis) and 4 mild/moderate events (one during pre-prophylaxis and three during prophylaxis). The reported success rate was 96.4% (96.8% for PUPs on pre-prophylaxis and 96.1% for PUPs on prophylaxis) and was comparable during the study main phase (97.8%) and extension period (93.9%). Furthermore, $> 90\%$ of bleeds were successfully treated with a single injection and > 2 injections were required for only 2 bleeding episodes. The ABR during prophylactic treatment in PUPs was lower compared to PTPs of the same age group (considering actual age; Poisson estimated ABR for main and extension phase of both studies was 0.65 [95%CI: 0.34; 1.25] and 1.02 [95%CI: 0.68; 1.54], respectively) and was lower during extension than during the main phase (Poisson estimated ABR was 0.82 [95%CI: 0.34; 1.98] during the main phase and 0.58 [95%CI: 0.35; 1.14] during study extension). It is further highlighted that

throughout the whole study period no target joint developed in PUPs (no target joint was present at study start).

After study protocol amendment 1 also major surgeries were allowed during the trial. A single major surgery in a <1 year old PUP was performed during trial 3895 (bilateral medial rectus recession) with a reported excellent haemostatic response after two additional doses of nonacog beta pegol.

Furthermore, 41 minor surgeries were performed in 21 patients with a total use of 34 additional doses of nonacog beta pegol and a median dose of 79.1 IU/kg during pre-prophylaxis (n=5 additional doses) and 46.5 IU/kg during prophylaxis (n=29 additional doses). It is noted that the median dose during pre-prophylaxis exceeds the planned dose of 40 IU/kg for minor surgeries by a factor of 2. Additional doses were given for port implantations as per protocol and on investigator's discretion. The choice can be followed and does not imply any (expected) lack of efficacy. Especially during pre-prophylaxis this decision appears reasonable considering that subjects were not yet following the standard prophylactic dosing schedule. As for study 3774, the haemostatic response to prophylactic treatment for minor surgeries was not recorded during study 3895 as per study protocol.

The median pre-prophylactic and prophylactic dose used (40.7 IU/kg and 44.1 IU/kg, respectively) as well as the median dose required to treat and stop bleeding events (41.2 IU/kg during pre-prophylaxis and 44.2 IU/kg during prophylaxis) was in line with the recommended dose during the study (i.e. 40 IU/kg). This observation supports the need for a single dose to treat the majority of bleeds (>90% were successfully treated with a single injection). The median annual consumption of 2312.2 IU/kg for PUPs is comparable to the median annual consumption in PTPs of the same age group (i.e. 2208.6 IU/kg) and is comparable to other FIX products with prolonged half-life.

The FIX inhibitor rate was 8% for PUPs during trial 3895 (n=4 of 50 patients). Inhibitor development is one of the main critical aspects regarding treatment initiation with FIX products in PUPs and the reported rate for trial 3895 is in line with reports of other FIX products used for PUPs. In total 7 patients were positive for anti-nonacog beta pegol antibodies (4 of those were high-titre antibodies concomitant with FIX inhibitor development and reduced FIX activity), 5 patients developed anti-CHO HCP antibodies and one patient was positive for anti-PEG antibodies at Visit 1 (i.e. prior to exposure to nonacog beta pegol). The immunogenic potential of nonacog beta pegol regarding anti-nonacog beta pegol antibodies, anti-CHO HCP antibodies and anti-PEG antibodies did not affect efficacy of the medication during the trial period in PUPs.

NN7999-4260

Supportive study

Data provided from trial 4260 indicate an increased Factor IX activity upon exposure to a single-dose of 50 IU/kg nonacog beta pegol compared to the same dose of ALPROLIX. Both medications were given as i.v. bolus injections to patients with haemophilia B with a FIX activity $\leq 2\%$ and without inhibitors. It is noted that all patients included in trial 4260 were ≥ 21 years of age. Thus, data from this trial are considered supportive information, but are not relevant for the concluded benefit risk of this variation, which addresses the extension of the indication for Refixia to treat paediatric patients ≤ 12 years of age. Furthermore, the direct comparison of PK parameters across studies is limited since patients in trial 4260 were dosed with 50 IU/kg versus 40 IU/kg for trials 3747 and 3774.

It is to be noted that possible assay interference, leading to over- or underestimation, was concluded for both FIX therapies during licensure, which was dependent on reagents and/or reference standards used (e.g. silica-based aPTT reagents appear better suitable for ALPROLIX, which on the other hand leads to overestimation of nonacog beta pegol activity; see EPARs and SmPCs of Alprolix and Refixia

for more detailed information). The MAH apparently considered this aspect by using a variety of assay setups. From available background information, the one-stage clotting assay seems more prone to possible interference. Thus, the chromogenic assay is considered more suitable for the direct comparison provided here. PK endpoints were derived using non-compartmental methods. Presented data indicate higher FIX activity levels after single dose nonacog beta pegol compared to ALPROLIX throughout the assay setups used. Still, the difference was considerably less pronounced with the chromogenic assay. Variations in assay setups used limits the possible comparison across trials and developmental programs. Published results for ALPROLIX in the EPAR regarding the time course of FIX activity levels after single exposure appear approximately in line with results presented for study 4260. Thus, despite limitation of the study it can be concluded that nonacog beta pegol appears to show a considerably higher FIX activity compared to ALPROLIX, at least after single infusion.

No safety signal arose from this single dose trial in adult subjects.

2.4.3. Conclusions on the clinical efficacy

The presented long-term data support the conclusion that nonacog beta pegol elevates FIX activity in paediatric patients to a level that allows the control over bleeding events in paediatric patients with haemophilia B (PTPs and PUPs). Thus, dosing recommendations appear to suit the demand for the prophylactic treatment (i.e. once weekly dosing with 40 IU/kg). Presented results for paediatric patients are also considered favourable when compared to results for other prolonged half-life FIX products that are licensed in the EEA for this age group. The recommended dose for treatment of bleeding episodes (40 IU/kg for mild/moderate bleeding and 80 IU/kg for severe bleeding) appears suitable and can be followed. It is concluded that the reported efficacy results together with the measured FIX activity at steady state (i.e. trough levels pre-dose) in the mild haemophilia range support the treatment of previously treated as well as previously untreated paediatric patients.

2.5. Clinical safety

Introduction

In the EU, the initial MA for nonacog beta pegol (Refixia) was received on 02 June 2017 and indicated for treatment and prophylaxis of bleeding in patients aged 12 years and above with haemophilia B (congenital factor IX deficiency). The safety profile during the initial evaluation of the product revealed the following:

- The most common side effects observed in clinical trials were nausea, pruritus, fatigue and injection site reactions. Most of the adverse events were of mild severity and considered unrelated to nonacog beta pegol. Available safety data derived in clinical trials with nonacog beta pegol, although limited with regards to the number of patients, treatment duration and absence of specific monitoring for PEG-associated adverse events, did not reveal any signals hinting to negative effects of PEG accumulation.
- Repeat dose toxicity studies in monkeys and rats revealed PEG present in choroid plexus of the brain (but not in other brain structures) whereas PEG alone studies demonstrated in addition vacuolation within macrophages in certain tissues in the same animal species. This was explained by accumulation of 40K PEG which is not easily broken down appearing histologically as vacuoles.

Based on evidence presented in the initial dossier, a possible impact of accumulation of PEG on function of affected tissues/organs after long-term treatment could not be excluded with reasonable

certainty. In consequence, the label was granted for adults and children ≥ 12 years of age, in whom most neurodevelopmental milestones are already reached.

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

- ☐ Trial 4260 – phase 1 pharmacokinetics (PK) of nonacog beta pegol vs. Alprolix (eftrenonacog alfa) in adults
- ☐ Trial 3774 ongoing extension phase – phase 3 trial in previously treated patients (PTPs) ≤ 12 years
- ☐ Trial 3895 ongoing main and extension phases – phase 3 trial in previously untreated patients (PUPs) < 6 years
- ☐ Study 4031 ongoing - global post-authorisation safety study (PASS) in previously treated children, adolescents and adult patients
- ☐ Study 4404 ongoing - post-marketing surveillance (PMS) study in previously treated children, adolescents and adult patients in Japan.

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

- ☐ PEG plasma concentration (in Trials 3747, 3775, 3774 and 3895).
- ☐ Neurological examination (NE) (in Trials 3774 and 3895).
- ☐ Neurocognitive assessments (NCAs) (in Trials 3774 and 3895).
- ☐ Collection of all CNS-related AEs and renal AEs as MESIs (in Trials 3774 and 3895)
- ☐ Determination of eGFR as a renal biomarker (in Trials 3774 and 3895).

Patient exposure

Safety data from the phase 3 Trials 3747, 3773, 3775 and 3774 in PTPs as well as from the first human dose Trial 3639 in PTPs, where 6 patients continued to Trial 3747, are pooled, including safety during surgery.

The cut-off date for inclusion of data for ongoing trials 3774 and 3895 was 25 November 2020 and updated according to the latest interim clinical trial reports for trial 3774 (CTR finalised on 03 September 2021) and 3895 (CTR finalised on 09 September 2021).

The following information relates to the pool of PTPs based on Trials 3639, 3747, 3773, 3775 and 3774:

- ☐ For patients who transferred from one trial to another, the last visit in the first trial was identical to the first visit in the following trial. In these cases, the exposure time for the overlapping day is calculated only once.
- ☐ In Trial 3775, patients could change their treatment regimen during the trial and thus contribute data in different treatment regimens.
- ☐ In the surgery trial (Trial 3773), all exposure is included as surgery-related exposure including exposure during the preoperative period and also exposure related to treatment of bleeds. In the extension trial (Trial 3775), surgery-related exposure is calculated as the time from the preoperative

loading dose until the time where the patient returned to the treatment regimen that he followed prior to a major surgery.

□ Exposure during minor surgery is included in the pool of either prophylactic or on-demand exposure depending on which treatment regimen the patient followed.

□ For exposure, baseline demographics and AEs (overall, SAEs, by relation to trial product and by severity), results in the pool of PTPs are presented by age (younger children 0-6 years, older children 7-12 years, adolescents 13-17 years and adults ≥ 18 years). For the summary of exposure, results are presented by age at inclusion (i.e. age of the patient at first visit in the first nonacog beta pegol trial) or using duration of exposure within each age span, as applicable. For the summary of baseline characteristics, results are presented by age at inclusion. For the summary of AEs, results are presented by actual age of the patient at onset of the AE. This approach is due to the long duration of Trial 3774, implying that paediatric patients became adolescents or adults during the trial (in the 0-6 year age group, 10 patients turned 7-12 years including 2 patients who further turned 13-17 years; in the 7-12 year age group, 10 patients turned 13-17 years including 3 patients who further turned ≥ 18 years old).

□ Only one of the patients was elderly (defined as 65 years of age and older) at the time of inclusion. This patient is included in the age group of adults ≥ 18 years.

□ Clinical laboratory evaluations, vital signs and physical examinations are described on a trial-by-trial basis.

The safety results of the phase 3 Trial 3895 in PUPs are presented separately (except for NE and NCA data) since patients in this trial were previously untreated compared with all the other trials.

Exposure in paediatric PTP trial 3774-EXT

Patient disposition

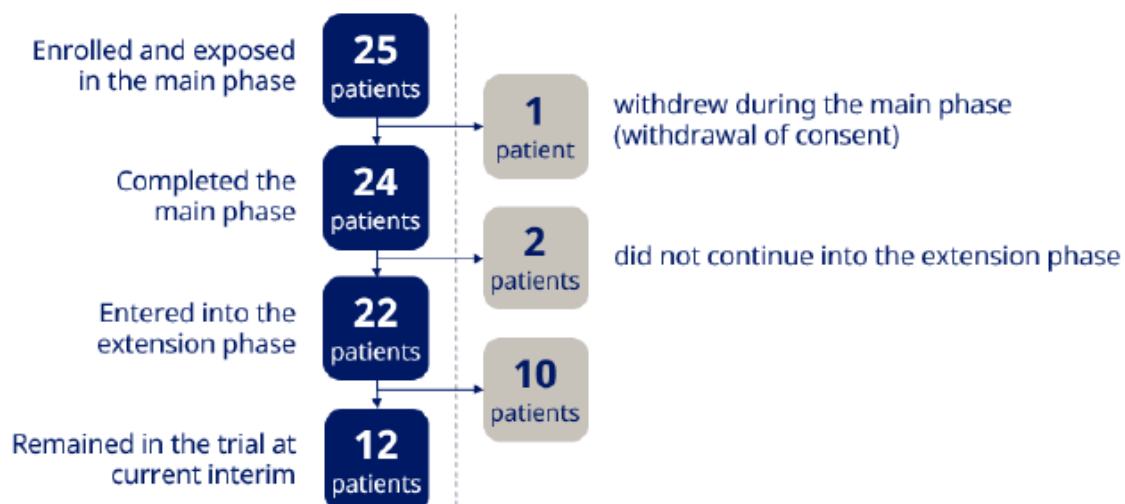


Figure 15: Patient disposition

Data cut-off date (extension phase): 25 November 2020 (interim cut-off date for clinical database); 08 February 2021 (interim database lock and cut-off date for Argus safety database).

One (1) patient withdrew consent during the main phase. Of the 24 patients who completed the main phase, 22 patients (88%) entered the extension phase (11 patients in each age groups) while 2 patients did not continue into the extension phase. The two patients fulfilled withdrawal criteria # 5 (5. Incapacity or unwillingness to follow trial procedures).

Of the 22 patients, 12 patients remained in the trial and 10 patients withdrew during the extension phase as of interim cut-off. None of the patients withdrew due to AEs. All withdrawn patients contributed with data until the date of withdrawal. The FAS and SAS consisted of 25 patients.

Table 36 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)	339.4 (134.4)	296.9 (141.0)	317.3 (136.7)
Median	394.5	359.0	391.0
Min ; Max	10.0 ; 419	53.0 ; 437	10.0 ; 437
Total number of exposure days per patient			
N	12	13	25
Mean (SD)	339.2 (134.3)	296.5 (141.1)	317.0 (136.7)
Median	394.5	358.0	391.0
Min ; Max	10.0 ; 419	53.0 ; 436	10.0 ; 436

Given the long duration of the combined main and extension phases with an average treatment period of 6.03 years, 10 of the 12 patients enrolled in the 0-6 year age group grew into 7-12 years including 2 patients who further grew into adolescents (13-17 year age group). Likewise, of the 13 patients enrolled in the 7-12 year age group, 10 patients grew into adolescents including 3 patients who further grew into adults. Thus, the trial included 12 adolescent patients and 3 adult patients.

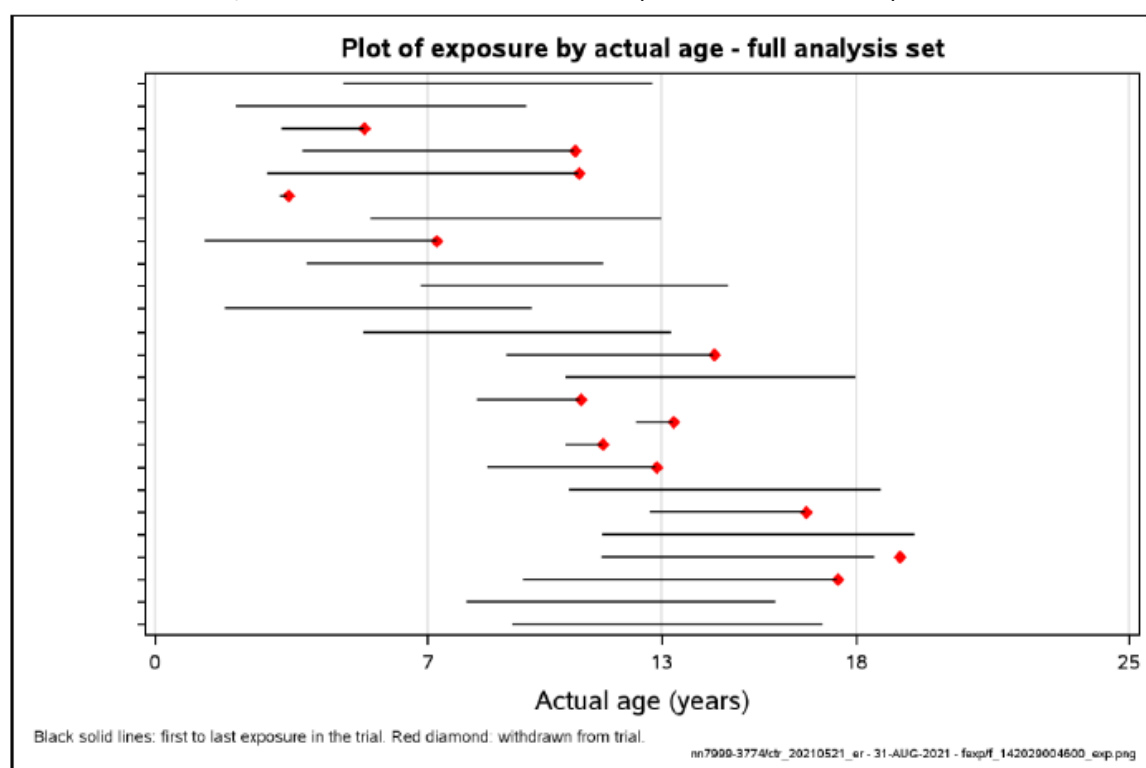


Figure 16 Plot of exposure by age – full analysis set

Trial 3774

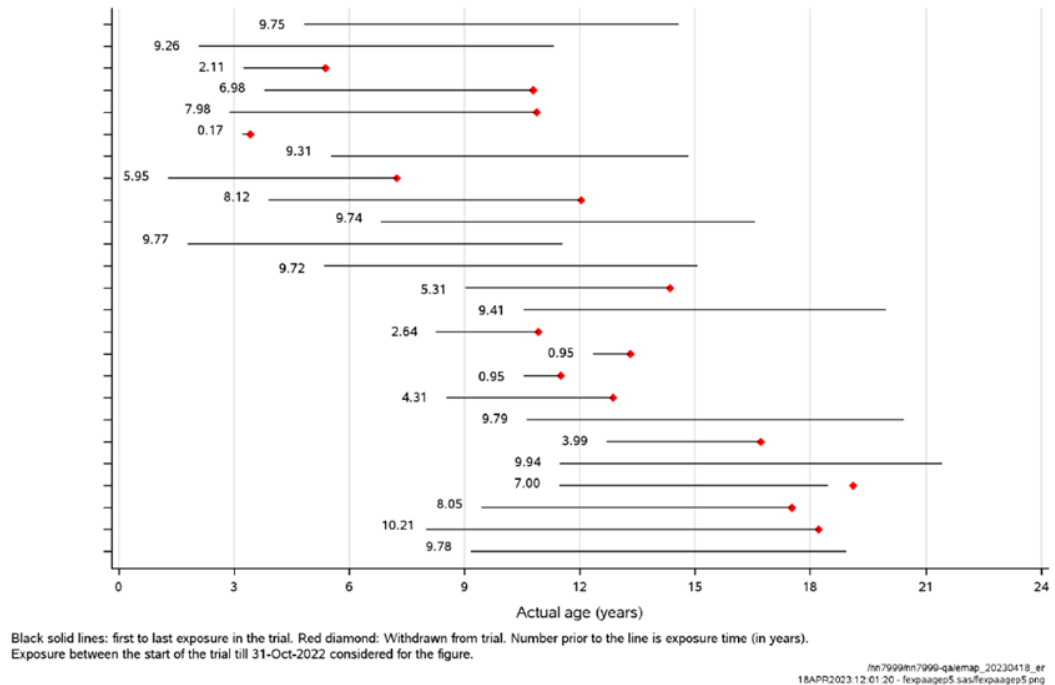


Figure 17 Plot of exposure by actual age – NN7999-3774 – full analysis set

Table 37 Exposure days and years in trial by actual age groups – Trial 3774

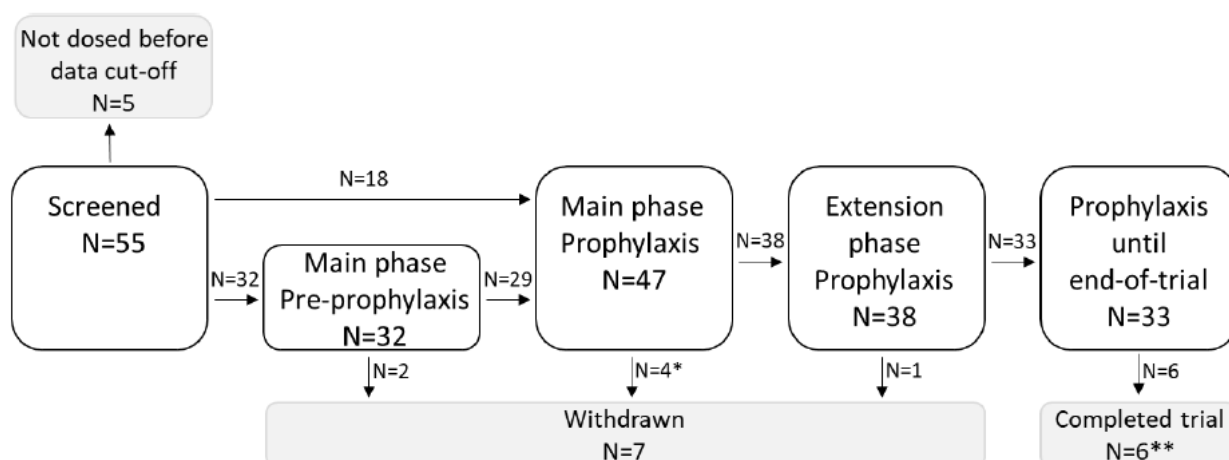
	0-6 year age group	7-12 year age group	13-17 year age group	18-70 year age group	Total
Number of patients	12	23	14	6	25
Exposure days	1815	4176	2558	491	9040
Years in trial	34.20	79.21	48.77	10.02	172.21

Cross-reference: Modified from Appendix 2, Table 14

Exposure in PUP trial 3895-EXT

Data cut-off date: 25 November 2020 (data cut-off date); 09 February 2021 (interim database lock and cut-off date for Argus safety database).

As of the interim cut-off date, 50 patients were exposed to nonacog beta pegol for a total of 6709 EDs, and the corresponding mean (SD) ED per patient was 134.2 (92.8) Eds. The cumulative exposure time in the trial was 142.3 years, and the corresponding mean (range) exposure period per patient was 2.85 (0.17–6.11) years. The majority of EDs and exposure time in trial were for prophylaxis treatment (mean Eds: 135.4, mean/range exposure time: 2.56 years, 0.06–6.06) relative to pre-prophylaxis treatment (mean Eds: 10.8, mean/exposure time: 0.69 years, 0.02–1.95). Out of the 38 patients who continued in the extension phase, 31 patients had been exposed to >100 Eds.

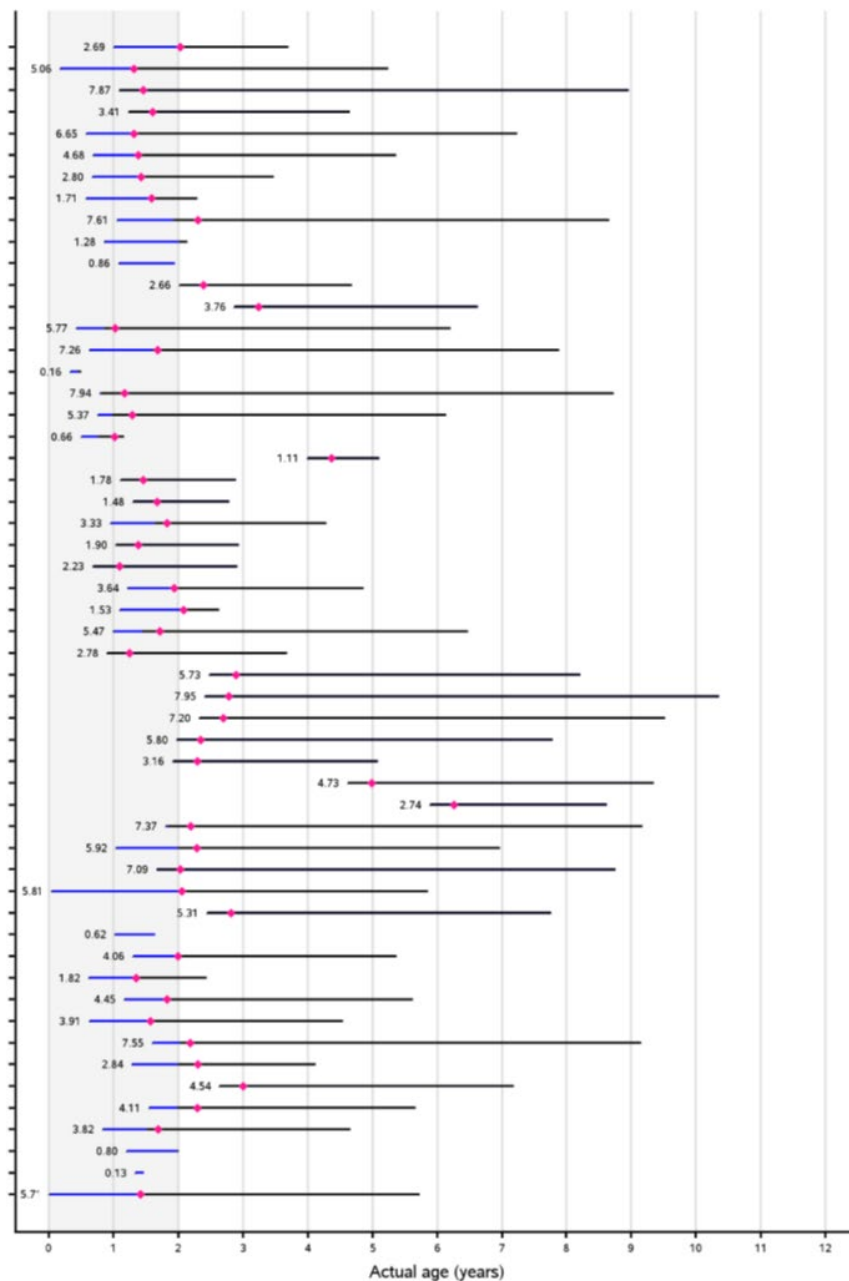


Main phase was completed when the patient had achieved 50 exposure days in trial at visit 23. Extension phase was completed when the patient had achieved 100 exposure days in trial at visit 28. Numbers in boxes describe the number of patients within each phase. Numbers between boxes describe the patient flow within the trial. *One patient withdrew after completion of the main phase and before entering the extension phase. **One patient discontinued treatment after completion of the extension phase and counted as completer of the trial.

Figure 18 Patient flow – all patients

A total of 32 patients in the age range of 0–1 years started on pre-prophylaxis treatment, and 18 patients started directly on prophylaxis treatment. A total of 29 patients switched from pre-prophylaxis to prophylaxis treatment. For the 47 patients on prophylaxis regimen period, the age range at entry was 0–5 years.

The MAH provided the exact number of patients who started directly with prophylaxis as well as the number of subjects who received pre-prophylaxis in PUP trial 3895. In addition, a plot was provided that depicts the time on pre-prophylaxis and prophylaxis for each subject. A substantial number of children <2 years of age (i.e. n=17) was exposed to weekly prophylaxis, and in addition 34 subjects <1 year of age started with pre-prophylaxis, of whom 20 received prophylaxis with longer dosing intervals and not only on-demand treatment of bleeds.



Blue lines: Pre-Prophylaxis exposure in trial. Black solid lines: Prophylaxis exposure in the trial.
Pink diamond: Represents 20 Exposure days.
Number prior to the line is exposure time (in years).
The figure shows exposure for the total duration of the trial.

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18APR2023 12:01:33 - fexppxp6.sas/fexppxp6.png

Figure 19 Plot of exposure with pre-prophylaxis and prophylaxis by actual age – NN7999-3895 - full analysis set

Table 38: nonacog beta pegol exposure- full analysis set

	Pre-prophylaxis	Prophylaxis	Total
Number of patients	32	47	50
Total number of doses per patient*			
N	32	47	50
Mean (SD)	10.9 (7.6)	135.9 (92.1)	134.7 (93.4)
Median	10.5	119.0	117.5
Min ; Max	1 ; 20	2 ; 324	3 ; 324
Total number of exposure days per patient			
N	32	47	50
Mean (SD)	10.8 (7.5)	135.4 (91.4)	134.2 (92.8)
Median	10.5	118.0	117.5
Min ; Max	1 ; 20	2 ; 324	3 ; 324

Table 39: Number of patients by exposure days – full analysis set

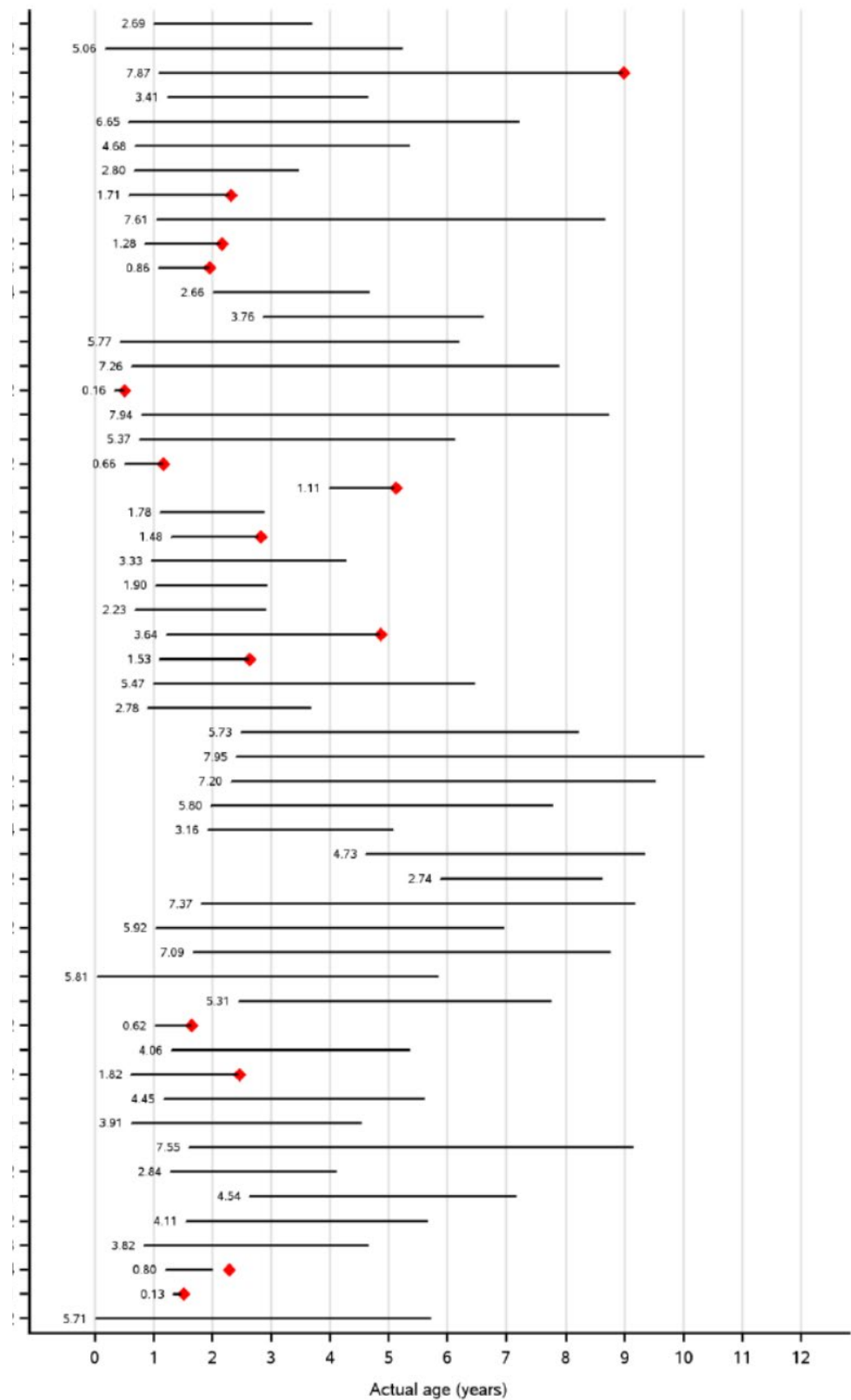
	Total N (%)
Patients exposed	50
0-25 EDs	7 (14.0)
26-50 EDs	5 (10.0)
51-100 EDs	7 (14.0)
101-200 EDs	21 (42.0)
>200 EDs	10 (20.0)

ED: exposure days.

N is the number of patients.

Trial 3895

The MAH provided data and narratives for all SAEs and MESIs that occurred since the last database lock in Feb 2021 to the latest database lock in Oct 2022. In addition, the MAH has provided updated exposure data for all subjects included in trial 3895, supported by tables and graphs.



Black solid lines: first to last exposure in the trial. Red diamond: Withdrawn from trial.
Number prior to the line is exposure time (in years).
The figure shows exposure for the total duration of the trial.

Figure 20 Plot of exposure by actual age – NN7999-3895 - full analysis set

Table 40 Exposure days and years in trial by pre-prophylaxis and prophylaxis treatment – Trial 3895

	Pre-prophylaxis	Prophylaxis	Total
Number of patients	34	51	54
Exposure days	371	10200	10571
Years in trial	24.28	193.72	218.00

Cross-reference: Modified from Appendix 2, Table 16

Adverse events

Trials in PTPs

An overview of AEs in PTPs is presented by age in Table 41.

A total of 1019 AEs were reported in 98 (85.2%) patients [3.5 AEs per PYE]. The rate of AEs was slightly higher in children aged 0-12 years than in adolescents and adults aged ≥ 13 years (Table 41). This difference was mainly driven by AEs concerning common childhood diseases.

Overall, the adverse event pattern was considered typical for the patient population. The most commonly reported AEs (reported in $>10\%$ of patients) were nasopharyngitis, cough, pyrexia, pain in extremity, contusion, arthralgia, headache, upper respiratory tract infection and influenza (Table 42).

The vast majority of the adverse events (98%) were non-serious. The majority of AEs were of mild or moderate severity across all age groups. A total of 17 AEs in 12 patients were severe. One of the severe events (hypersensitivity) was judged by the investigator as probably related to nonacog beta pegol, while the remaining severe AEs were judged as unlikely related to nonacog beta pegol.

A total of 37 AEs in 23 (20%) patients [0.1 AEs per PYE] were judged by the investigator as probably or possibly related to nonacog beta pegol. The majority of the events were non-serious, of mild or moderate severity and the majority of the patients recovered from their events. There were no obvious differences across age groups in the rate of these events. The most common AEs with possible or probable relation to nonacog beta pegol were fatigue and overdose. There were no obvious differences in AE frequency between races.

Table 41: Overview of adverse events by actual age – trials 3639, 3747, 3773, 3775 and 3774- safety analysis set

	0-6 years N(%) E[R]		7-12 years N(%) E[R]		13-17 years N(%) E[R]		18-70 years N(%) E[R]		Total N(%) E[R]	
Number of patients	12		23		30		81		115	
Total time in trial (years)	34.20		74.73		68.45		114.21		291.60	
Total number of exposure days	1815		3944		3615		5763		15137	
All adverse events	11 (91.7)	252[7.4]	20 (87.0)	309[4.1]	25 (83.3)	148[2.2]	62 (76.5)	310[2.7]	98 (85.2)	1019[3.5]
Serious adverse events	2 (16.7)	3[<0.1]	3 (13.0)	3[<0.1]	3 (10.0)	4[<0.1]	8 (9.9)	8[<0.1]	16 (13.9)	18[<0.1]
Adverse events by severity										
Mild	11 (91.7)	221[6.5]	20 (87.0)	288[3.9]	23 (76.7)	130[1.9]	57 (70.4)	239[2.1]	93 (80.9)	878[3.0]
Moderate	5 (41.7)	29[0.8]	9 (39.1)	21[0.3]	13 (43.3)	16[0.2]	31 (38.3)	58[0.5]	51 (44.3)	124[0.4]
Severe	1 (8.3)	2[<0.1]	-	-	2 (6.7)	2[<0.1]	9 (11.1)	13[0.1]	12 (10.4)	17[<0.1]
Adverse events by relationship										
Probably or possibly related	1 (8.3)	2[<0.1]	3 (13.0)	6[<0.1]	2 (6.7)	4[<0.1]	17 (21.0)	25[0.2]	23 (20.0)	37[0.1]
Unlikely related	11 (91.7)	250[7.3]	20 (87.0)	303[4.1]	25 (83.3)	144[2.1]	62 (76.5)	284[2.5]	98 (85.2)	981[3.4]
Adverse events Leading to withdrawal	-		-		-		2 (2.5)	2[<0.1]	2 (1.7)	2[<0.1]

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 patient years of exposure)

All adverse events in this table are treatment emergent. Linked adverse events are not included.

All treatment arms are pooled.

An exposure day is a day where the patient received at least one dose of nonacog beta pegol.

For Trial 3774, data are included until 25Nov2020.

Actual age is defined as the patients age at each assessment.

Table 42: Summary of most frequent (PT> 10%) adverse events – trials 3639, 3747, 3779, 3778 and 3774- safety analysis set

	Phase 1 Single dose		Prophylaxis Multiple dose		On-demand		Major surgery		Total	
	N (%)	E [R, F]	N (%)	E [R]	N (%)	E [R, F]	N (%)	E [R, F]	N (%)	E [R]
Number of patients	16		98		16		16		115	
Total time in trial (years)	1.40		275.52		13.34		1.34		291.60	
Total number of exposure days	16		14737		286		98		15137	
All adverse events	6 (37.5)	11 [7.9, 0.7]	86 (87.8)	939 [3.4]	12 (75.0)	50 [3.7, 0.2]	10 (62.5)	19 [14.2, 0.2]	98 (85.2)	1019 [3.5]
Injury, poisoning and procedural complications										
Contusion	-		16 (16.3)	38 [0.1]	1 (6.3)	1 [<0.1, <0.1]	-		17 (14.8)	39 [0.1]
Infections and infestations										
Nasopharyngitis	1 (6.3)	1 [0.7, <0.1]	21 (21.4)	55 [0.2]	-		-		22 (19.1)	56 [0.2]
Influenza	-		12 (12.2)	26 [<0.1]	1 (6.3)	1 [<0.1, <0.1]	-		13 (11.3)	27 [<0.1]
Upper respiratory tract infection	-		12 (12.2)	22 [<0.1]	2 (12.5)	5 [0.4, <0.1]	-		14 (12.2)	27 [<0.1]
Respiratory, thoracic and mediastinal disorders										
Cough	-		18 (18.4)	36 [0.1]	1 (6.3)	1 [<0.1, <0.1]	-		19 (16.5)	37 [0.1]
Musculoskeletal and connective tissue disorders										
Arthralgia	-		14 (14.3)	28 [0.1]	1 (6.3)	3 [0.2, <0.1]	-		15 (13.0)	31 [0.1]
Pain in extremity	-		15 (15.3)	24 [<0.1]	1 (6.3)	1 [<0.1, <0.1]	1 (6.3)	1 [0.7, <0.1]	17 (14.8)	26 [<0.1]
General disorders and administration site conditions										
Pyrexia	-		16 (16.3)	40 [0.1]	1 (6.3)	1 [<0.1, <0.1]	1 (6.3)	1 [0.7, <0.1]	18 (15.7)	42 [0.1]
Nervous system disorders										
Headache	-		13 (13.3)	29 [0.1]	2 (12.5)	3 [0.2, <0.1]	-		15 (13.0)	32 [0.1]

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 patient years of exposure)

F: Number of adverse events per exposure days (E/total number of exposure days)

Only preferred terms with adverse event rate more than 10% in Total column.

All adverse events in this table are treatment emergent. Linked adverse events are not included.

An exposure day is a day where the patient received at least one dose of nonacog beta pegol.

For Trial 3774, data are included until 25Nov2020.

Trial 3895

AE incidence

A total of 741 AEs were reported in 50 (100%) PUPs [5.21 AEs per PYE] (Table 43). The majority of AEs (721 AEs in 49 (98%) patients) were judged by the investigator as unlikely related to nonacog beta pegol.

Table 43 Overview of adverse events – Trial 3895– safety analysis set

	Pre-prophylaxis			Prophylaxis			Total		
	N (%)	E	[R]	N (%)	E	[R]	N (%)	E	[R]
Number of patients	32			47			50		
Total time in trial (years)	22.14			120.14			142.28		
Total number of exposure days	346			6363			6709		
All adverse events	26 (81.3)	131 [5.92]		46 (97.9)	610 [5.08]		50 (100.0)	741 [5.21]	
Serious adverse events	8 (25.0)	13 [0.59]		17 (36.2)	27 [0.22]		23 (46.0)	40 [0.28]	
Adverse events by severity									
Mild	25 (78.1)	106 [4.79]		41 (87.2)	534 [4.44]		47 (94.0)	640 [4.50]	
Moderate	8 (25.0)	17 [0.77]		25 (53.2)	63 [0.52]		28 (56.0)	80 [0.56]	
Severe	5 (15.6)	8 [0.36]		11 (23.4)	13 [0.11]		15 (30.0)	21 [0.15]	
Adverse events by relationship									
Probably or possibly related	3 (9.4)	5 [0.23]		7 (14.9)	15 [0.12]		10 (20.0)	20 [0.14]	
Unlikely related	26 (81.3)	126 [5.69]		44 (93.6)	595 [4.95]		49 (98.0)	721 [5.07]	
Adverse events									
Leading to withdrawal	2 (6.3)	3 [0.14]		3 (6.4)	3 [0.02]		5 (10.0)	6 [0.04]	

All adverse events in this table are treatment emergent and adverse events during follow-up are not included.

Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns.

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).

Overall, the adverse event pattern was considered typical for the patient population. The most common AEs (reported in >10% of patients) were pyrexia, upper respiratory tract infection, nasopharyngitis, cough, diarrhoea, vomiting, rhinorrhoea, ear infection, viral infection, fall, otitis media, influenza, rash, bronchitis and pneumonia (Table 44).

Table 44 Summary of most frequent (PT > 10%) adverse events – Trial 3895 – safety analysis set

	Pre-prophylaxis N(%) E[R]		Prophylaxis N(%) E[R]		Total N(%) E[R]	
Number of patients	32		47		50	
Total time in trial (years)	22.14		120.14		142.28	
Total number of exposure days	346		6363		6709	
All adverse events	26(81.3)	131[5.9]	46(97.9)	610[5.1]	50(100.0)	741[5.2]
Infections and infestations						
Nasopharyngitis	5(15.6)	12[0.5]	20(42.6)	53[0.4]	20(40.0)	65[0.5]
Upper respiratory tract infection	6(18.8)	8[0.4]	17(36.2)	30[0.2]	23(46.0)	38[0.3]
Ear infection	4(12.5)	5[0.2]	6(12.8)	8[<0.1]	8(16.0)	13[<0.1]
Otitis media	2(6.3)	2[<0.1]	5(10.6)	10[<0.1]	7(14.0)	12[<0.1]
Bronchitis	1(3.1)	2[<0.1]	5(10.6)	7[<0.1]	6(12.0)	9[<0.1]
Viral infection	3(9.4)	3[0.1]	5(10.6)	6[<0.1]	8(16.0)	9[<0.1]
Influenza	1(3.1)	1[<0.1]	6(12.8)	7[<0.1]	7(14.0)	8[<0.1]
Pneumonia	1(3.1)	1[<0.1]	5(10.6)	6[<0.1]	6(12.0)	7[<0.1]
General disorders and administration site conditions						
Pyrexia	11(34.4)	24[1.1]	23(48.9)	63[0.5]	30(60.0)	87[0.6]
Respiratory, thoracic and mediastinal disorders						
Cough	4(12.5)	5[0.2]	14(29.8)	26[0.2]	16(32.0)	31[0.2]
Rhinorrhoea	3(9.4)	5[0.2]	9(19.1)	20[0.2]	10(20.0)	25[0.2]
Gastrointestinal disorders						
Diarrhoea	3(9.4)	3[0.1]	11(23.4)	12[<0.1]	13(26.0)	15[0.1]
Vomiting	2(6.3)	2[<0.1]	8(17.0)	11[<0.1]	10(20.0)	13[<0.1]
Injury, poisoning and procedural complications						
Fall	2(6.3)	2[<0.1]	7(14.9)	13[0.1]	8(16.0)	15[0.1]
Skin and subcutaneous tissue disorders						
Rash	2(6.3)	2[<0.1]	6(12.8)	14[0.1]	7(14.0)	16[0.1]

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 patient years of exposure)

F: Number of adverse events per exposure days (E/total number of exposure days)

Only preferred terms with adverse event rate more than 10% in Total column.

All adverse events in this table are treatment emergent. Linked adverse events are not included.

An exposure day is a day where the patient received at least one dose of nonacog beta pegol.

For Trial 3895, data are included until 25Nov2020.

The vast majority of the adverse events (95%) were non-serious. The majority of the AEs were mild or moderate (Table 43). A total of 21 AEs in 15 patients were severe, of which 4 events were judged by the investigator as probably or possibly related to nonacog beta pegol.

A total of 20 AEs reported in 10 (20%) patients [0.14 AEs per PYE] were judged by the investigator as probably or possibly related to nonacog beta pegol (Table 43). Most of the events were non-serious, of mild or moderate severity and the majority of the patients recovered from their events. The most common AEs with possible or probable relation to nonacog beta pegol were FIX inhibition, hypersensitivity and rash.

Four (4) AEs of FIX inhibitor were reported in 4 patients. These AEs were all possibly or probably related to nonacog beta pegol as judged by the investigator, and they were all serious, moderate or severe and not recovered.

Three (3) AEs of hypersensitivity were reported in 2 patients. These AEs were all possibly or probably related to nonacog beta pegol as judged by the investigator. Two (2) of these AEs were reported for a patient who also reported FIX inhibition. These hypersensitivity AEs were all moderate or severe and were all recovered.

Four (4) AEs of rash were reported in 1 patient. These AEs were all probably related to nonacogbeta pegol as judged by the investigator, all were non-serious, of mild severity and recovered.

The remaining 9 AEs reported in 6 patients that were judged by the investigator to be possibly or probably related to nonacog beta pegol were reported as single PTs only (infusion site extravasation, pyrexia, hypoacusis, conjunctivitis, accidental underdose, language disorder, autism spectrum disorder, drug hypersensitivity, anaphylactic reaction).

There were no obvious differences in AE frequency between races.

Adverse events related to major surgery

Trials in PTPs

AEs related to major surgery are included in the total pool of AEs described above. None of the AEs related to major surgery gave rise to safety concerns.

Trial in PUPs

There was one major surgery with no AEs.

No safety signal arises from AEs reported after major or minor surgery.

Serious adverse event/deaths/other significant events

SAE

Trials in PTPs

A total of 18 SAEs in 16 (13.9%) patients [<0.1 AEs per PYE] were reported. The SAEs were mostly recorded as single events and across different SOC. The SAEs occurred after 1–379 EDs of nonacog beta pegol, and no association between frequency of the events and exposure time was observed.

One (1) severe SAE of hypersensitivity was judged by the investigator as probably related to nonacog beta pegol), while the remaining SAEs were judged by the investigator as unlikely related to nonacog beta pegol. This hypersensitivity event occurred in a patient in the first human dose trial 3639 and was already assessed during the initial dossier submission.

The majority of the patients recovered from their SAEs, while 1 event had a fatal outcome (hepatocellular carcinoma) and 2 events (skin ulcer and Tourette's syndrome) had the outcome 'not recovered'.

Trial in PUPs

A total of 40 SAEs were reported in 23 (46.0%) patients [0.28 SAEs per PYE]. Half of the SAEs were recorded in the SOC Infections and infestations, which is generally expected in a paediatric population. The remaining SAEs were recorded across different SOC and all SAEs were mostly reported as single events. The SAEs occurred after 1–241 EDs of nonacog beta pegol, and no association between frequency of the events and exposure time was observed. The majority of SAEs (32 out of 40) were

judged by the investigator as unlikely related to nonacog beta pegol while 8 SAEs in 6 patients were judged by the investigator as probably or possibly related to nonacog beta pegol.

These related AEs included 4 AEs of FIX inhibitor (not recovered), 1 AE of anaphylactic reaction (recovered), 1 AE of hypersensitivity (recovered), 1 AE of language disorder (not recovered) and 1 AE of autism spectrum disorder (ASD; not recovered).

The majority of patients had recovered from their SAEs (32), while 1 SAE (spontaneous ICH with associated seizures) had a fatal outcome and 7 SAEs had an outcome stated as 'not recovered'.

Deaths

Trials in PTPs

One (1) fatal AE was reported in Trial 3775. A 42-year-old patient was diagnosed with metastatic stage IV hepatocellular carcinoma after 499 days in the trial programme and died after 570 days. During the trial programme he had been exposed to nonacog beta pegol for 72 EDs. The patient had a history of hepatitis B and C and hepatic cirrhosis and as such at risk for development of hepatocellular carcinoma. The event was evaluated as unlikely related to nonacog beta pegol by the investigator and Novo Nordisk.

No other fatal events occurred during the clinical trials with nonacog beta pegol in PTPs.

Trial in PUPs

One (1) fatal AE was reported in Trial 3895. The very young child was enrolled on pre-prophylaxis. The investigator judged this fatal AE of ICH to be unlikely related to exposure to nonacog beta pegol, while development of (non-confirmed) FIX inhibitors was judged by the investigator as possibly related to nonacog beta pegol.

Other Significant Events

Adverse events related to the theoretical safety concern of PEG

AEs that might theoretically be related to PEG following exposure to nonacog beta pegol were identified through a broad search. The SMQ searches 'acute renal failure' and 'drug-related hepatic disorders' were chosen because the kidneys and the liver are known sites of PEG elimination. The NNMQ search 'CNS events' consisting of the SOCs Nervous system disorders and Psychiatric disorders was chosen based on nonclinical data showing presence of PEG in the choroid plexus of the brain. CNS-related AEs were to be reported as MESIs in Trials 3774 and 3895 from December 2017 upon implementation of protocol amendments for both trials. Renal AEs were to be reported as MESIs in Trials 3774 and 3895 from June 2018 upon implementation of protocol amendments for both trials.

Renal adverse events

Trials in PTPs

A total of 2 renal disorder AEs (proteinuria and renal impairment) were reported in 2 (1.7%) patients. Both events were non-serious and judged by the investigator as unlikely related to nonacog beta pegol.

Trial in PUPs

The SMQ search did not identify any renal disorder AEs.

Hepatic adverse events

Trials in PTPs

A total of 11 hepatic AEs were reported in 7 (6.1%) patients. Three (3) of the 7 patients were hepatitis C positive at entry into the trial, of which 1 patient reported 3 events of abnormal liver parameters which is expected for this population, since a significant number of adult patients with haemophilia B were infected with hepatitis C via administration of pooled factor concentrates, cryoprecipitate or fresh frozen plasma in the 1970s and early 1980s.

In addition, 1 event of abnormal prothrombin level, 1 event of prolonged prothrombin time, 1 event of hepatic pain and 1 event of increased INR were reported in 3 hepatitis C negative patients, all of which were judged unlikely related to nonacog beta pegol and had an outcome of recovered. One hepatic AE (hepatocellular carcinoma) was fatal.

Trial in PUPs

One event of non-serious moderate hepatic function abnormal was reported. The event was judged by the investigator as unlikely related to nonacog beta pegol and had an outcome of recovered.

The reported hepatic AEs were evaluated by Novo Nordisk as unlikely to be a clinical consequence of long-term exposure to PEG.

CNS-related adverse events

Trials in PTPs

A total of 52 CNS-related AEs in 30 (26.1%) patients [0.2 AEs per PYE] were reported. The most commonly reported event was headache (32 events in 15 patients), gait disturbance (3 events in 3 patients) and speech disorder (2 events in 1 patient). All other AEs were events of single occurrence.

All 52 AEs identified in the search were non-serious and of mild or moderate severity, except 1 AE of Tourette's disorder which was reported as serious. The majority of the AEs were judged by the investigator as unlikely related to nonacog beta pegol, except 5 AEs that were judged by the investigator as probably or possibly related: 3 events of headache in 3 patients and 2 events of speech disorder in 1 patient. All 5 events were mild and had an outcome of recovered.

Headache

All 32 events of headache were non-serious and most were mild and judged by the investigator as unlikely related to nonacog beta pegol. None of the events led to withdrawal from treatment and the outcome of all events was recovered or recovering. The majority of the events (22 out of 32) were reported within the patient's first 100 EDs and all events occurred within 1–9 days after the last dose of nonacog beta pegol. The duration of headache ranged from 1 to 6 days for most events, while 4 events had a duration of 18, 23, 27 and 61 days.

For 16 of the 32 events of headache, other AEs which could give rise to headache, were reported within +/- 7 days of the headache. These events were: body aches (4 events), nasopharyngitis (3), fever (3), nausea (3), vomiting (3), upset stomach (2), fatigue (2), sore throat (1), earache (1), rhinorrhoea (1) and tiredness (1).

The reported AEs of headache were evaluated by Novo Nordisk as unlikely to be a clinical consequence of long-term exposure to PEG, as most events were of short duration and the patients recovered while continuously being treated with nonacog beta pegol. For 50% of the AEs of headache, other AEs occurred within +/- 1 week, pointing to alternative aetiologies of the headache.

Trial in PUPs

A total of 35 CNS-related AEs in 15 (30.0%) patients [0.2 AEs per PYE] were reported. The most common AEs (on PT level) were speech disorders developmental (5 AEs in 5 patients), sleep disorder (8 AEs in 1 patient) and headache (5 AEs in 1 patient). All events, except 4 cases of speech disorder developmental, had the outcome recovered. Febrile convulsion and intracranial haemorrhage were each reported in 2 patients, while all other AEs were events of single occurrence.

The majority of the 35 CNS-related AEs identified in the search were non-serious, of mild or moderate severity and judged by the investigator as unlikely related to nonacog beta pegol.

Four CNS-related events in 4 patients were SAEs (2 events of intracranial haemorrhage (ICH), 1 event of autism spectrum disorder (ASD) and 1 event of language disorder). Three of these SAEs were severe (2 ICH and 1 ASD) of which 1 event of ICH had a fatal outcome. Two of the SAEs (in 2 patients) were judged by the investigator as probably or possibly related to nonacog beta pegol (ASD and language disorder).

Most patients recovered from the CNS-related AEs; however, due to the natural course of language development, a few patients with speech delays had not recovered at the interim cut-off date.

Two CNS-related SAEs (ASD and language disorder) in 2 patients in Trial 3895 were judged by the investigator to be probably or possibly related to nonacog beta pegol. PEG plasma levels for the 2 patients were within the observed mean steady state range for all patients in Trial 3895 (i.e., 4.7 to 6.4 µg/mL) and both patients had a low number of EDs at the time of AE onset (87 and 46 EDs). For comparison, the assumed time to steady state in the human choroid plexus, as identified in nonclinical modelling studies, corresponds to approximately 250 EDs in a clinical trial setting of once-weekly dosing. The NCA outcomes collected from these 2 patients were considered invalid due to use of interpreter.

A very young child was enrolled on pre-prophylaxis. An AE of suspected autism was reported after having received 87 EDs of nonacog beta pegol. No abnormalities were noted at the time of enrolment. According to the patient's mother, the patient's aunt (sister of his father) was diagnosed with oligophrenia (diagnosis not confirmed). The patient was born in gestational week 39. The patient did not react normally to verbal or visual orders, showed increasingly aberrant behaviour and no social interaction and hypoacusis was reported as a non-serious AE. The hypoacusis was revealed as not present after myringotomy. The patient visited the Neuropediatric service, confirming the diagnostic impression of autism spectrum disorder and was requested for genetic studies, array and study of fragile X chromosome. The genetic report revealed that fragile X chromosome syndrome was not present. Genetic analyses were planned. The event was upgraded to serious by the investigator (seriousness criteria 'persistent or significant disability/incapacity' and 'important medical event') based on a request from Novo Nordisk to re-evaluate the seriousness of the condition. The event was categorised as 'possibly related' to treatment with nonacog beta pegol by the investigator and the patient was withdrawn. In agreement with the patient's family, it was decided to keep him in the trial for follow-up. The patient was treated with another recombinant FIX product and was to be followed by scheduled visits of 6-months intervals at the trial site. Additionally, the patient was to be followed by regular assessments in a neuro-paediatric department and the diagnosis stayed unchanged.

A very young child diagnosed with haemophilia B, was enrolled on pre-prophylaxis. The patient was delivered by caesarean section with no complications or defects at birth. Two minor head traumas and respiratory tract infections had been reported for the patient since birth. According to the patient's mother, the patient's aunt (sister of his father) was diagnosed with oligophrenia (diagnosis not confirmed). The patient had a brother diagnosed with ASD. The patient visited the Neuro-paediatrician. After the neurologic and clinical exploration, he was diagnosed with a chronic language disorder and suspicion of ADHD after 1.5 years in the trial and 46 EDs in trial. The event was categorised as moderate in severity and treatment was discontinued. The patient was referred to follow-up with a neuro-paediatrician for confirmation of chronic language delay and, due to the young age of the patient, referred for further follow-up on age-appropriate diagnosis of ADHD. The patient switched to a commercial FIX product. The patient had a normal growth development according to his age.

Following request, the MAH clarified that the 2 patients are siblings.

Autism has a rather complex pathogenetic background which is not yet completely understood and no clear relationship between ASD and nonacog beta pegol or PEG exposure can be reasonably established. A recent study from the United Kingdom found a significantly higher prevalence of ASD in boys with haemophilia compared with the general population and unaffected boys aged 8 years (Bladen M et al. Haemophilia. 2020; 26(S4):13). Speech disorder represents a commonly occurring developmental phenomenon in childhood and genetic or environmental factors may play a role in the aetiology. Based on the currently available information, Novo Nordisk evaluates the above 2 events of ASD and language disorder to be unlikely related to nonacog beta pegol.

Sleep disorders

A total of 8 AEs of sleep disorder were reported in 1 patient. All 8 events were mild and judged by the investigator as unlikely related to nonacog beta pegol. These events were reported in a child over a period from February 2019 to January 2020. All events were of 1 or 2 days' duration, and the outcome was recovered for all events. For 5 of the 8 events, the event of sleep disorder was reported together with other AEs that negatively influences sleep: cough, catarrh, pyrexia, sore head, sore throat, sore mouth, suspected worms and blocked nose.

Speech disorders

A total of 8 AEs related to speech delay or language disorders were reported in 8 patients. The majority (7 out of 8 events) were non-serious, mild or moderate and judged by the investigator as unlikely related to nonacog beta pegol. Three of the patients had recovered or were recovering from the event at the time of data cut-off. Of the remaining 5 patients, 1 had a medical history of hearing difficulties, unclear speech, frequent ear infections, developmental delays in talking and understanding, and a family history of neurological disease, emotional problems, learning disability, and behaviour problems. One patient had an ICH prior to the event. The remaining 3 patients had 46, 53 and 84 EDs at the time of onset of the event. Modelling based on nonclinical studies indicate that it takes 4.5 years to achieve steady state concentrations of PEG in choroid plexus. This corresponds to approximately 250 EDs in a clinical trial setting of once-weekly dosing, i.e. a considerably higher number of EDs than received at onset of these 3 events of speech disorders.

Novo Nordisk evaluates that there is no indication that any of the AEs captured by the NNMQ search 'CNS events' are clinical consequences of long-term PEG exposure. In some cases, information is available that points to an alternative aetiology (including medical or family history). In other cases,

few EDs at the time of onset of the event, the short duration of the event and the full recovery during continuous treatment with nonacog beta pegol all point to an alternative explanation.

Evaluation of risks associated with long-term exposure to PEG

This section presents an evaluation of the CNS-related AEs and neurological and neurocognitive findings in relation to exposure and PEG plasma concentrations for patients in Trials 3774 and 3895.

CNS-related AEs were reported in all age groups, regardless of number of exposure days. PEG plasma levels for patients with CNS-related AEs in PTPs and PUPs ranged from 0.1 to 8.1 µg/mL (mean steady state concentration ranged from 4.7 to 6.9 µg/mL in these trials). Occurrence of CNS-related AEs did not seem to be related to peaks in PEG plasma levels.

Most CNS-related AEs occurred before 4.5 years of exposure which is the time to steady state in the human choroid plexus, as identified in nonclinical modelling studies. Thus, data from Trials 3774 and 3895 did not indicate any correlation between PEG plasma levels and occurrence of CNS-related AEs.

Most patients recovered from the CNS-related AEs; however, due to the natural course of language development, a few patients with speech delays had not recovered at the interim cut-off date. Two CNS-related SAEs (ASD and language disorder) in 2 patients in Trial 3895 were judged by the investigator to be probably or possibly related to nonacog beta pegol. PEG plasma levels for the 2 patients were within the observed mean steady state range for all patients in Trial 3895 (i.e., 4.7 to 6.4 µg/mL, Trial 3895-EXT) and both patients had a low number of EDs at the time of AE onset (87 and 46 EDs). For comparison, the assumed time to steady state in the human choroid plexus, as identified in nonclinical modeling studies, corresponds to approximately 250 EDs in a clinical trial setting of once-weekly dosing. The NCA outcomes collected from these 2 patients were considered invalid due to use of interpreter.

Autism has a rather complex pathogenetic background which is not yet completely understood and no clear relationship between ASD and nonacog beta pegol or PEG exposure can be reasonably established. A recent study from the United Kingdom found a significantly higher prevalence of ASD in boys with haemophilia compared with the general population and unaffected boys aged 8 years (Bladen M, et al., 2020). Speech disorder represents a commonly occurring developmental phenomenon in childhood and genetic or environmental factors may play a role in the aetiology. Based on the currently available information, Novo Nordisk evaluates the above 2 events of ASD and language disorder to be unlikely related to nonacog beta pegol.

Most NEs were evaluated as normal. The abnormal neurological findings pertained almost exclusively to abnormal language and were often consistent with pre-existing language delay. A total of 5 (13%) patients reported shifts down in language skills (Trial 3895), and this rate is comparable to that of speech/language delays in children under the age of 5 years in the general population (Law J, et al., 2000). In eTHINK, abnormal or delayed 'language skills' and developmental 'milestones' were found in more than 5% of the population, and this was mainly seen in the younger age groups.

The NCAs comprised the qualitative evaluations of neurodevelopment, cognitive performance, behavioural function, adaptive skills, executive function and attention and processing speed. Overall, no consistent pattern was observed in these standardised, regularly repeated cognitive assessments, and performance was generally comparable to that of the eTHINK population.

Cognitive outcomes seemed to be independent of PEG exposure; hence, for patients assumed to be at steady state (i.e. patients with > 250 EDs), no noticeable deviations from the general pattern was

observed. No clear relation between change in categorisation of 'clinical concern' and drug exposure or PEG plasma concentration was seen.

Results from Trial 3895 confirmed that most paediatric patients with severe haemophilia start therapy early in life, at an age where few neurological and NCAs are applicable. In these patients, it is difficult to obtain neurological and neurocognitive responses that, to a sufficient extent, can be used to assess long-term safety outcome measures within the same patient. Instead, Novo Nordisk followed a generally accepted practice and compared neurological and neurocognitive performance with age-matched controls, i.e the eTHINK population. This was done using an extensive neurological and neurocognitive programme designed to capture neurodevelopmental changes and deficits known to exist in patients with haemophilia. Using this method, it was possible to investigate whether patients treated with nonacog beta pegol reached the same milestones as the general haemophilia population. Testing was done with brief intervals to accommodate age-related neurodevelopmental fluctuations in the maturing brain. Results from Trial 3895 showed no consistent pattern in terms of neurocognitive performance and overall, the pattern was similar to that of the eTHINK population.

In conclusion, the NEs and NCAs did not give rise to safety concerns, and no indications of any neurodevelopmental deficits or CNS-related AEs caused by long-term exposure to nonacog beta pegol was found.

Laboratory findings

Trial 3774-EXT

The mean (SD) values of eGFR for 12 patients in the 0-6 year age group was 139.4 (32.8) mL/min and the mean (SD) values of eGFR for 13 patients in the 7-12 year age group was 105.2 (10.0) mL/min.

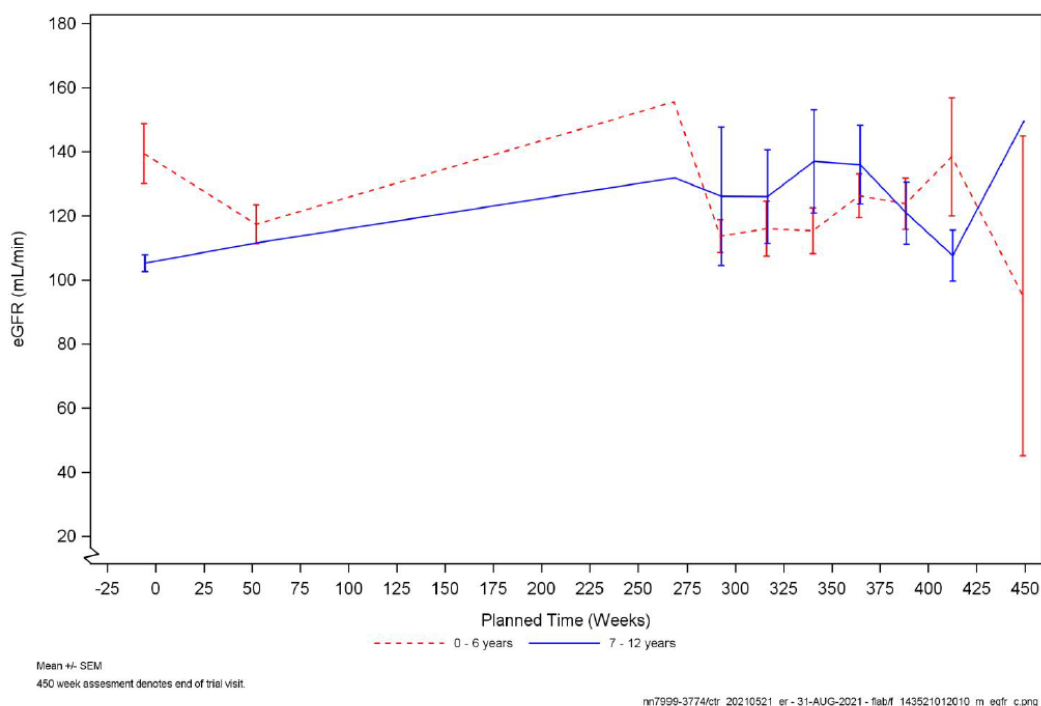


Figure 21 Biochemistry – mean profiles of eGFR (mL/min) - safety analysis set

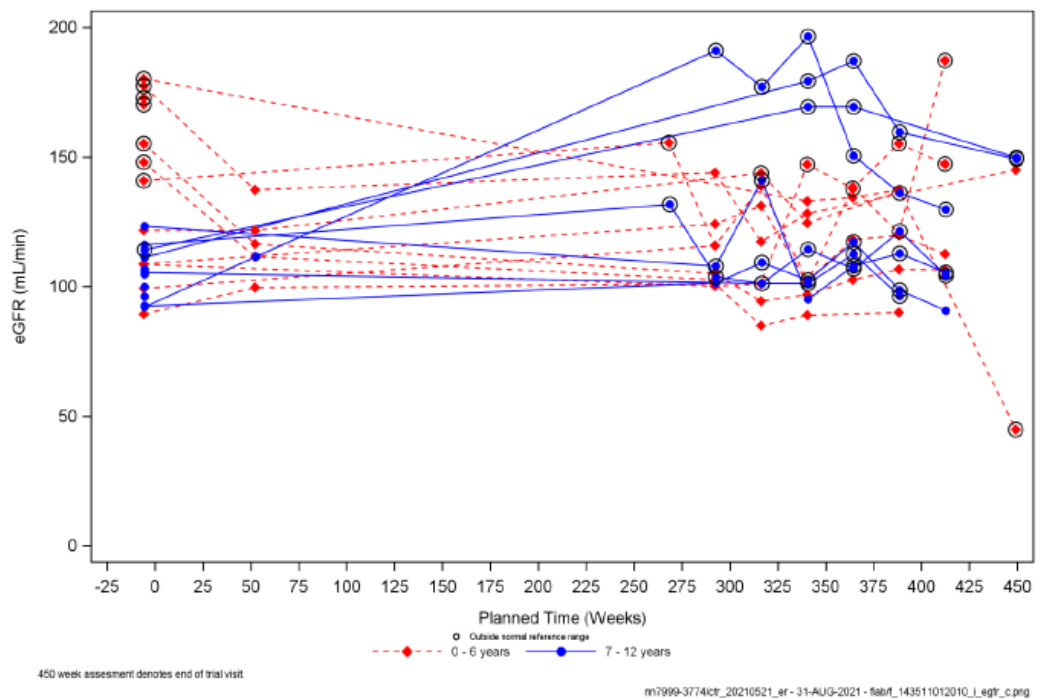


Figure 22 Biochemistry – individual profiles of eGFR (mL/min) - safety analysis set

One patient had eGFR values >90 ml throughout trial 3774 and 3774-EXT, but at the End of trial visit reported a value of 44.92. No additional information regarding these eGFR values in this patient is available. However, no other clinical data imply an influence of nonacog beta pegol on renal function.

/Prophylaxis 40 IU/kg	eGFR	Visit 1 screening	180.24	mL/min	95.490279106- H
					163.69762133
		Visit 24	132.97	mL/min	80.529692279-
					146.84826239-
		Visit 25	134.32	mL/min	81.747285347-
					149.06857916
		Visit 26	137.29	mL/min	83.181001689-
					151.68300308
		End of trial	44.92	mL/min	84.144837974- L
					153.44058689

Trial 3895-EXT

The mean eGFR profile was within the level of normal kidney function (> 90 mL/min) throughout the trial and did not decrease over time.

Less variability for eGFR is observable for PUPs in trial 9895 than for PTPs in trial 3774.

No safety signal arises from the eGFR values observed in the two studies.

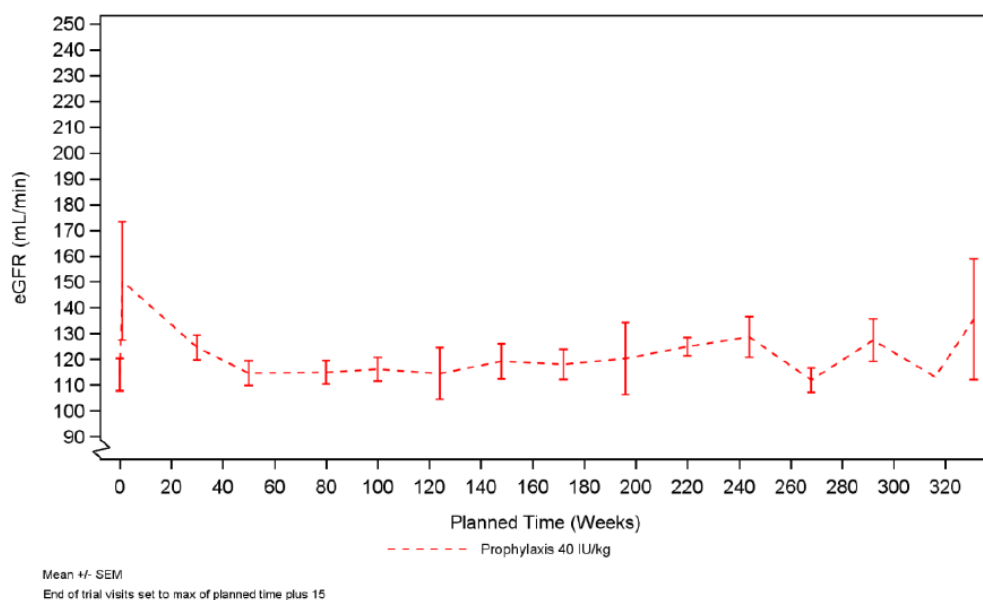


Figure 23 Biochemistry – mean profiles of egfr (mL/min) - safety analysis set

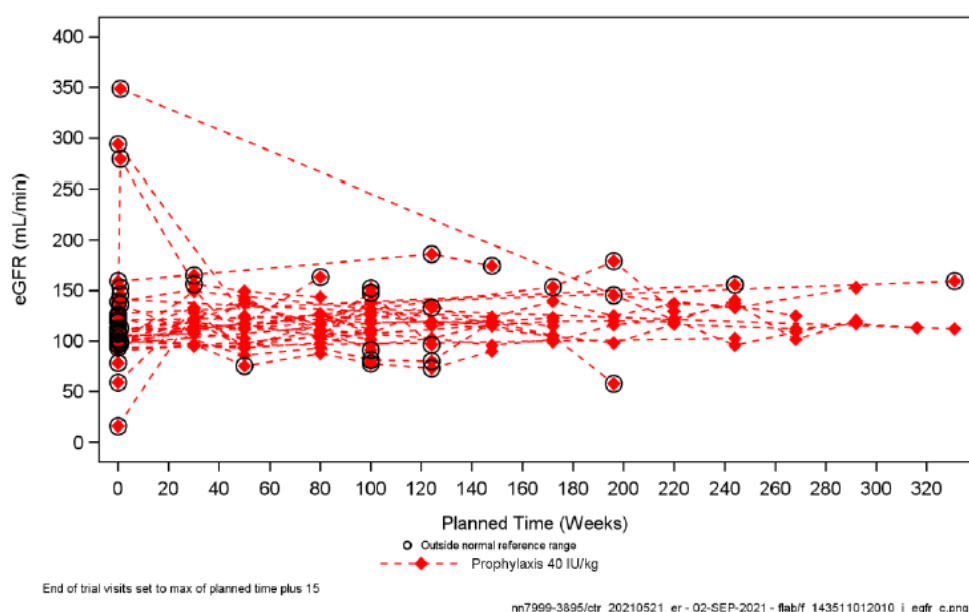


Figure 24 Biochemistry – individual profiles of egfr (mL/min) - safety analysis set

FIX inhibitors

Trials in PTPs

None of the 115 patients in the pool of PTPs had any positive FIX inhibitor samples (≥ 0.6 BU). Furthermore, none of the 15 PTPs in Trial 4260 had any positive FIX inhibitor samples (≥ 0.6 BU). Thus, no PTPs developed FIX inhibitors.

Trial in PUPs

In Trial 3895, 4 out of the 50 PUPs developed FIX inhibitors. The estimated inhibitor rate was 8.0% (1-sided 97.5% upper CI: 21%). Three (3) out of these 4 patients developed high-titre inhibitors within 5 EDs and 1 patient developed low-titre inhibitors after 27 EDs. Two (2) of the 3 patients who developed high-titre inhibitors were exposed to other rFIX product(s) than nonacog beta pegol prior to their

positive inhibitor test. The patient who developed low-titre inhibitors was also treated with another rFIX product prior to participation in the trial.

An additional (fifth) patient developed low-titre non-confirmed inhibitors.

Other antibodies

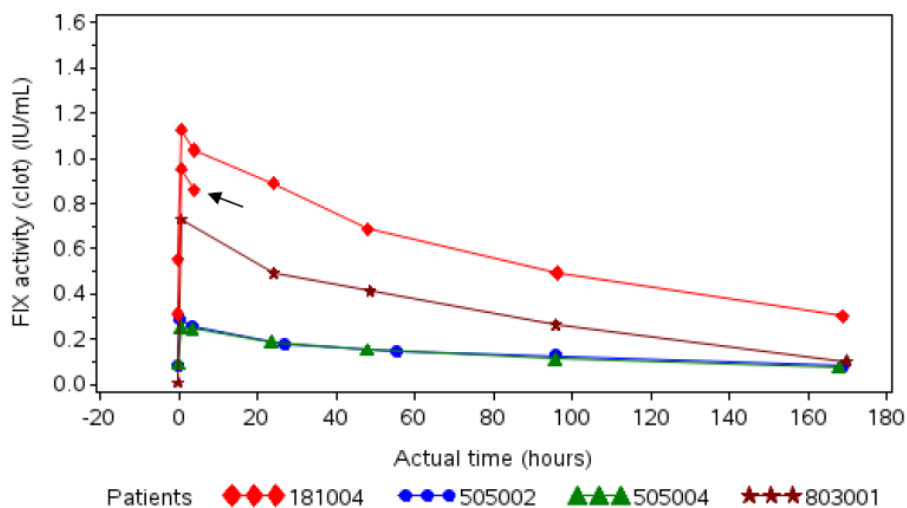
Assessments of non-neutralising anti-nonacog beta pegol antibodies were done in all trials and assessments of anti-CHO HCP antibodies were done in Trials 3747, 3773, 3774, 3775 and 3895. In Trial 3639, testing for anti-CHO HCP antibodies was only performed in cases of allergic/anaphylactic reactions or inhibitor development.

Trials in PTPs

In Trials 3747, 3773, 3774 and 3775, 4 PTPs were positive for anti-nonacog beta pegol antibodies, of which 2 were already positive prior to exposure to nonacog beta pegol. None of the anti-nonacog beta pegol binding antibodies had any inhibitory effect, and patients were only transiently positive. Overall, detection of antibodies did not correlate with any AEs or reduced FIX activity levels.

PK profiles for the 4 patients with antibodies against nonacog beta pegol are shown in Figure 25 on linear scale. The PK profiles did not show any signs of reduced FIX activity when compared to mean plasma FIX activity profiles at steady state.

One Patient (40 IU/kg) had an incomplete PK profile assessment at an unscheduled visit but was re-assessed one week later at another unscheduled visit. Anti-nonacog beta pegol antibody assessments were performed at scheduled visits, and showed negative results. Accordingly, no increased risk of unfavourable effects associated with immunogenicity was identified in PTPs.



Arrow: Incomplete PK profile assessment.

Figure 25 PK profile for patients having at least one positive nonacog beta pegol binding antibody measurement – Trials 3747, 3775 and 3774 – safety analysis set

A total of 5 PTPs had positive tests with low titres for anti-CHO HCP antibodies. One of these patients was positive prior to dosing with nonacog beta pegol. All positive anti-CHO HCP antibodies were low-titre, and none of these were reported as AEs.

Positive anti-PEG antibodies were indirectly concluded in those samples with positive anti-nonacog beta pegol binding antibodies and no cross-reactivity to rFIX. A total of 4 PTPs were indirectly tested positive for anti-PEG antibodies. One of these patients was positive prior to dosing with nonacog beta pegol. All post-dose positive anti-PEG antibodies were low-titre and transient, with no clinical signs or symptoms or reduced FIX activity levels associated.

Overall, detection of antibodies in PTPs did not correlate with any AEs or reduced trough FIX activity levels. Accordingly, no increased risk of unfavourable effects associated with immunogenicity was identified in PTPs.

Trial in PUPs

A total of 7 PUPs were positive for anti-nonacog beta pegol binding antibodies. Four (4) patients developed persistent high titre anti-nonacog beta pegol binding antibodies concomitant with FIX inhibitor development and reduced FIX activity, while 2 other patients developed transient low titre anti-nonacog beta pegol binding antibodies. One patient was only positive prior to exposure to nonacog beta pegol.

A total of 5 PUPs were positive for anti-CHO HCP antibodies, of which 1 patient was only positive prior to dosing with nonacog beta pegol. All positive anti-CHO HCP antibodies were low-titre. In 1 PUP, the positive test for anti-CHO HCP antibodies occurred at the same time as AEs of anaphylactic reaction and factor IX inhibition. Two weeks later at the EOT visit, the patient was negative for anti-CHO HCP antibodies. In the other patients, there were no clinical signs or symptoms associated with the positive anti-CHO HCP tests.

Positive anti-PEG antibodies were indirectly concluded in those samples with positive anti-nonacog beta pegol binding antibodies and no cross-reactivity to rFIX. The only sample positive for anti-PEG antibodies was prior to exposure to nonacog beta pegol (low-titre).

Overall, there was no increased risk of unfavourable effects associated with immunogenicity identified in PUPs.

Haematology, biochemistry, coagulation-related parameters and urinalysis

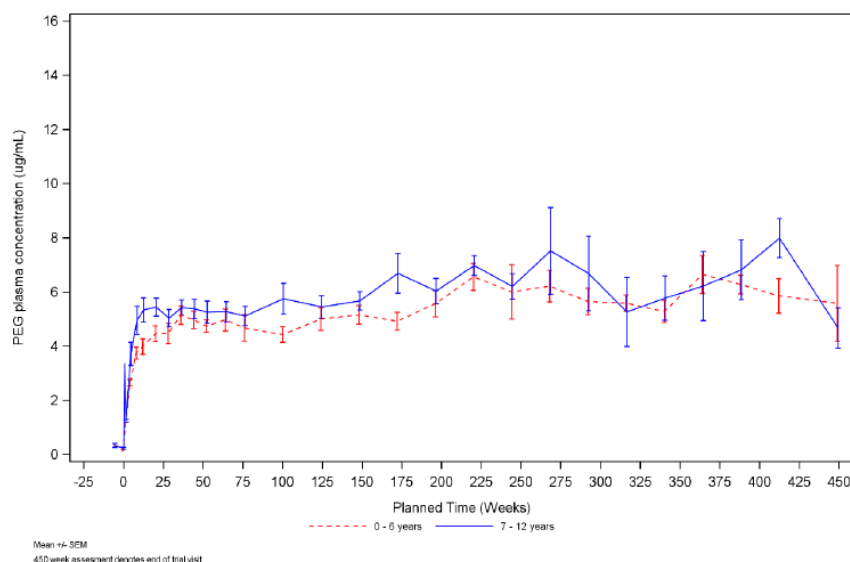
Overall, no clinically relevant changes associated with exposure to trial product have been observed for parameters of haematology, biochemistry, coagulation-related parameters and urinalysis in any of the clinical trials with nonacog beta pegol.

PEG plasma concentration

The nonclinical finding that PEG is present in choroid plexus epithelial cells has raised concerns about long-term exposure to nonacog beta pegol and potential neurodevelopmental sequelae in children. It is therefore important to provide reassurance that PEG steady state concentrations in patients treated with nonacog beta pegol will be well below the PEG concentration where no toxicities, no PEG-related vacuolation, and no cellular changes have been observed in the nonclinical chronic toxicity studies in rats. Consequently, measurements of PEG plasma levels were implemented in Trials 3774 and 3895 prospectively from December 2017 as well as measured in additional historic visit samples in Trials 3747 and 3775 if consented and available, i.e. full profiles are not available for all patients.

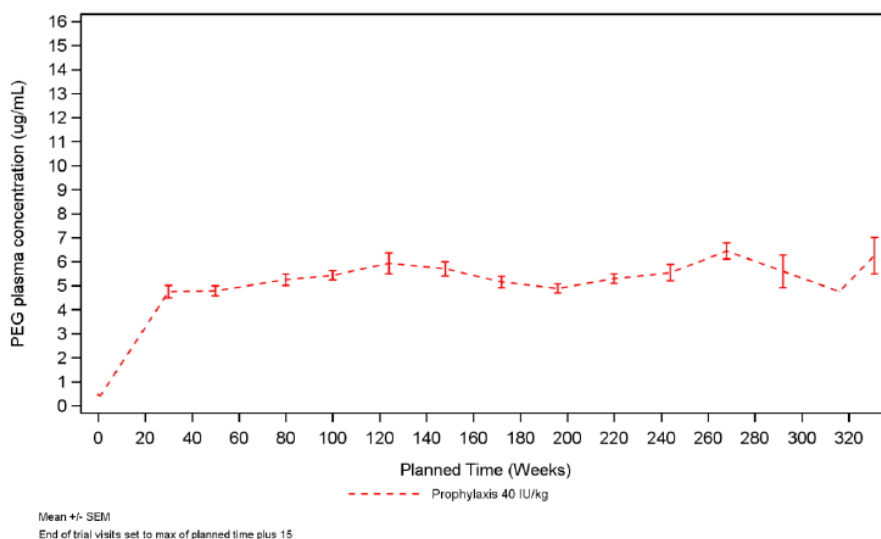
In both Trials 3774 and 3895, PEG plasma concentrations reached steady state after approximately 6 months in patients on prophylactic treatment (Figure 26 and Figure 27). Following this timepoint, the PEG plasma concentrations remained at the steady state level until last measurement during treatment. The mean steady state PEG plasma concentration ranged from 4.7-6.9 µg/mL.

In Trial 3774, the mean and individual PEG plasma concentration-time profiles indicated that the PEG plasma concentration was slightly higher in the 7-12 years age group than in the 0-6 years age group (Figure 26), corresponding to a physiologically expected decrease in renal clearance of nonacog beta pegol occurring with increasing age.



Data are mean $\pm$ standard error of the mean.

Figure 26 PEG – mean profiles of PEG plasma concentration (ug/mL) – Trial 3774 - safety analysis set



Data are mean $\pm$ standard error of the mean.

Figure 27 PEG – mean profiles of PEG plasma concentration (ug/mL) – Trial 3895 - safety analysis set

The mean PEG plasma concentration-time profile from Trials 3747 and 3775 was based on historic visit samples and was therefore shorter than the one seen in Trial 3774. Still, the PEG plasma concentration-time profile in Trials 3747 and 3775 (Figure 28) was comparable with the profile seen in Trial 3774. However, for some time points PEG plasma concentration was slightly higher in Trials 3747 and 3775, which is in alignment with the minor increase in PEG plasma concentration with increasing age described above.

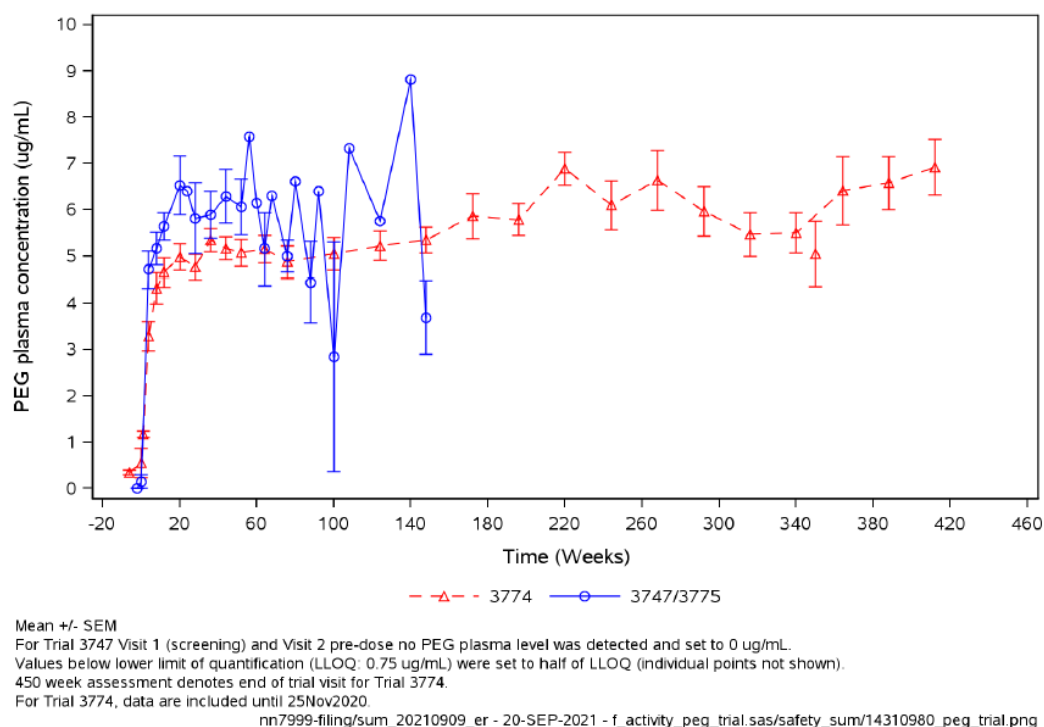


Figure 28 Mean profiles of PEG concentration (ug/mL) – Trials 3747/3775 and 3774 - safety analysis set

Safety in special populations

Neurological and neurodevelopmental evaluations in paediatric subjects

The presence of PEG in choroid plexus epithelial cells is a nonclinical finding which has raised concerns about long-term exposure to nonacog beta pegol and potential neurodevelopmental sequelae in children. To address this issue in a structured manner, protocol amendments were implemented to monitor PEG plasma concentrations, to capture all CNS related AEs as MESIs, and to perform twice-yearly age-appropriate NEs and NCAs. Further, to collect more neurological and neurocognitive data, the recruitment period was extended to include un-exposed patients aged 0-6 years (Trial 3895).

In developmental neuroscience, studies with cross-sectional designs have frequently been used to generate knowledge about the degree to which specific neural characteristics and processes are presented within certain age groups (Guyer AE, *et al.*, 2018), and striking differences do exist between age groups in specific functional domains (e.g., reward signals and emotions increase brain activity in adolescence relative to childhood) (Chein J, *et al.*, 2011; Guyer AE, *et al.*, 2008). Thus, brain development is a dynamic process of growing, creating new connections and further developing its capacity to process information. These processes are dependent on age and individual experiences as well as elimination of extra synapses during early childhood and adulthood ('synaptic pruning') (Guyer AE, *et al.*, 2018). Both linear and nonlinear performance patterns have been found during early brain maturation at repeated testing during infancy (MacNeill LA, *et al.*, 2018).

Due to the different timing of neuronal maturation in different regions it becomes difficult to compare an initial cognitive assessment with a subsequent assessment within the same individual. As an example, working memory cannot be accurately measured in a 1-year-old, and as working memory develops over time, comparing working memory in a 3-year-old with that of the same child as 5-year-old will not give any indications of whether or not the child is following a normal developmental path.

A neurological baseline seems also difficult to establish as many of the NEs are age-specific (e.g. gait cannot be measured in the very young patients who are not yet walking). In addition, neurological sequelae have been reported in 39% of patients with ICH, impacting outcome of later NEs, such as language, in these patients (Chalmers EA, et al., 2018).

To overcome the difficulty in establishing a baseline for NEs and neurocognitive function, Novo Nordisk has developed a normative dataset of neurological, neurocognitive and neurobehavioral performance in a cross-sectional study, i.e. the eTHINK study (HAEM-4436). This normative dataset provides an age-matched control population comprising children and young adults with haemophilia to which patients in Trials 3774 and 3895 can be compared. Haemophilia patients were chosen for the normative dataset as a longitudinal study has shown that impaired neurological and neurocognitive performance occur more frequently in haemophilia patients (Loveland KA, et al., 1994; Sirois PA, et al., 1998). The eThink study enrolled 551 male subjects with haemophilia A or B up to 21 years of age.

Based on the current knowledge of brain maturation and disease pattern in haemophilia patients, a carefully selected battery of NCAs, designed by an external vendor with expertise in neuropsychological testing, was implemented in Trials 3774 and 3895. The selected battery was designed to capture subtle changes in e.g. attention, processing speed and executive functioning. Testing was done with brief intervals to mitigate the impact of age-related fluctuations, change in age-related instruments (i.e. progression from Cogstate Paediatric to Cogstate Adult battery), impact of joint bleeds on gait and to capture safety signals. An overview of the instruments applied to evaluate neurological, neurocognitive and neuro-behavioural function is provided in Table 45.

Table 45 Instruments used to evaluate neurological, neurocognitive and neuro-behavioural function and development

Patient age (years: months)	Examination	Neurodevelopment and cognitive performance	Behavioural	Adaptive behaviour	Executive function	Attention processing speed
1:00 to 1:11	Neurological Exam	Bayley-III		ABAS-3 Parent 0-5y		
2:00 to 3:6			BASC-3 PRS-P 2-5y (Parent)		BRIEF-P Parent 2:0-5:11y	
4:0 to 5:11		WPPSI-IV				Cogstate Custom Paediatric Battery (4-9y)
6:0 to 6:11			BASC-3 PRS-C 6-11y (Parent)	ABAS-3 Parent 5-21y	BRIEF-2 Parent 5-18y	
7:0 to 7:11		WASI-II				
8:0 to 9:11			BASC-3 PRS-C 6-11y (Parent) BASC-3 SRP-C 8-11y			
10:0 to 10:11						Cogstate Custom Adult Battery (10-21y)
11:0 to 11:11					BRIEF-2 Parent 5-18y BRIEF-2 SR 11-18y	
12:0-15:11			BASC-3 PRS-A 12-21y (Parent)			
16:0-17:11			BASC-3 SRP-A 12-21y	ABAS-3 Parent 5-21y ABAS-3 Adult 16-89y		
18:0-21:11			BASC-3 PRS-A 12-21y (Parent) BASC-3 SRP College 18-25y		BRIEF-A Adult 18-90y	

Abbreviations: A= adolescent (for BASC)/adult (for BRIEF); ABAS-3 = Adaptive Behaviour Assessment System, Third Edition; BASC-3 = Behaviour Assessment System for Children, Third Edition; Bayley = Bayley Scales of Infant and Toddler Development, Third Edition; BRIEF = Behaviour Rating Inventory of Executive Function; C = Child; Cogstate = Cogstate Computerized Battery; PRS = parent rating scale; P = Preschool; SR = Self-report; SRP = self-rating of personality; WASI-II = Wechsler Abbreviated Scale of Intelligence, Second Edition; WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition; y = years

Cross-reference: HAEM-4436, eTHINK study (M 5.3.5.4), Table 9-1.

Neurological and Neurocognitive Assessments in PTP trial 3774 and PUP trial 3895

Neurological examinations

Neurological examination was included as a result of protocol amendment no. 9, version 2.0 (01 December 2017) in trial 3774 and as a result of protocol amendment 5 (11 December 2017) in trial 3895.

Following aspects of age-appropriate neurological examinations were assessed:

- ☐ General appearance including language, social and developmental aspects, handedness, head circumference and level of consciousness
- ☐ Cranial nerves in relation to sight including pupillary reaction to light, visual fields and acuity, and eye movements, facial sensation and movement, hearing, palate sound and tongue movement and trapezius muscle function
- ☐ Tone of truncal, upper and lower extremity right and left
- ☐ Strength of upper and lower extremity right and left
- ☐ Reflexes of biceps, triceps, knee and ankle jerk, all right and left as well as Babinski
- ☐ Sensory aspect of cold, pin prick, light touch and proprioception (tor up/down)
- ☐ Gait with regards to walking, running, on heels and toes, tandem (toe/heel walk), standing or hop one leg/foot right and left, and Romberg sign
- ☐ Coordination and fine motor including finger-to-nose, rapid index finger tab and rapid finger movement right and left.

Any pre-existing physical or neurological finding that was present at the time of enrolment in the trial were reported as medical history, new abnormal findings or any changes in the findings which fulfilled the criteria of an AE were recorded as such.

Neurocognitive assessments

Neurocognitive assessments were included as a result of protocol amendment 10 (27-June-2018) in trial 3774 and as a result of protocol amendment 6 (29 June 2018) in trial 3895.

A set of comprehensive instruments for the neurocognitive assessments were employed. An overview of these instruments, and the age groups in which they were to be used, is provided in Table 46. A short description of the instruments, and how they were used in this study, is provided in Table 47.

Table 46 Instruments used and neurological examinations and neurocognitive assessments

Patient age (years: months)	Examination	Neurodevelopment and cognitive performance	Behavioural	Adaptive behaviour	Executive function	Attention processing speed
1:00 to 1:11	Neurological Exam	Bayley-III		ABAS-3 Parent 0-5y		
2:00 to 3:6			BASC-3 PRS-P 2-5y (Parent)		BRIEF-P Parent 2:0-5:11y	
4:0 to 5:11		WPPSI-IV		ABAS-3 Parent 5-21y	BRIEF2 Parent 5-18y	Cogstate Custom Paediatric Battery (4-9y)
6:0 to 6:11		BASC-3 PRS-C 6-11y (Parent)				
7:0 to 7:11		WASI-II			BRIEF2 Parent 5-18y BRIEF2 SR 11-18y	Cogstate Custom Adult Battery (10-21y)
8:0 to 9:11			BASC-3 PRS-C 6-11y (Parent) BASC-3 SRP-C 8-11y			
10:0 to 10:11					BRIEF-A Adult 18-90y	
11:0 to 11:11			BASC-3 PRS-A 12-21y (Parent) BASC-3 SRP-A 12-21y	ABAS-3 Parent 5-21y ABAS-3 Adult 16-89y		
12:0-15:11						
16:0-17:11						
18:0-21:11		BASC-3 PRS-A 12-21y (Parent) BASC-3 SRP College 18-25y				

Abbreviations: A= adolescent (for BASC)/adult (for BRIEF); ABAS-3 = Adaptive Behaviour Assessment System, Third Edition; BASC-3 = Behaviour Assessment System for Children, Third Edition; Bayley = Bayley Scales of Infant and Toddler Development, Third Edition; BRIEF = Behaviour Rating Inventory of Executive Function; C = Child; Cogstate = Cogstate Computerized Battery; PRS = parent rating scale; P = Preschool; SR = Self-report; SRP = self-rating of personality; WASI-II = Wechsler Abbreviated Scale of Intelligence, Second Edition; WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition; y = years

Table 47 Description of instruments of neurocognitive examinations and their use

Instrument	Description	Type of test	Application in this trial	Scores
Bayley-III Bayley Scales of Infant and Toddler Development – Third Edition	Measure of neurodevelopment including infants' memory and ability to habituate to visual and auditory stimuli. This assessment include cognitive, language, motor, social-emotional, and adaptive behavioural domains. Designed for individuals of ages 1 to 42 months.	Administered by psychologist Questionnaire completed by the parents.	Patients aged (years:months): 1:0 to 3:6. English-speaking countries at every second NCA.	The Bayley-III instrument is summarised by the following composite scores assessed by performance based test of the child: • Cognition composite score • Communication composite score ◦ Receptive communication ◦ Expressive communication • Motor composite score ◦ Fine motor ◦ Gross motor Together with one composite score assessed through a parent questionnaire: • Social-emotional composite score The adaptive behavioural scale was not performed in this trial to avoid duplication with the ABAS instrument.
WPPSI-IV Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition	Measure of cognitive intelligence. Designed for individuals of ages 4:0 to 7:7 years:months.	Administered by psychologist	Patients aged (years:months) 4:0 to 6:11. English-speaking countries at every second NCA.	The WPPSI-IV instrument is summarised by the full scale IQ composite score which is derived from the following index scales and subtests: • Verbal Comprehension Index ◦ Information subtest ◦ Similarities subtest • Block design subtest • Matrix reasoning subtest • Picture memory subtest • Bug search subtest
WASI-II Wechsler Abbreviated Scale of Intelligence – Second Edition	Abbreviated measure of cognitive intelligence. Designed for individuals of ages 6 to 90 years.	Administered by psychologist	Patients aged (years:months): 7:0 to 10:11. English-speaking countries at every second NCA.	The WASI-II instrument is summarised by the full scale IQ composite score which is derived from the following index scales and subtests: • Verbal Comprehension Index ◦ Vocabulary subtest ◦ Similarities subtests • Perceptual Reasoning Index ◦ Block Design subtest ◦ Matrix Reasoning subtests
BASC-3 Behavioural Assessment System for Children – Third Edition	Measure of emotional behaviour and self-perceptions. This multidimensional assessment is used to identify emotional and behavioural problems through two components: Parent Rating Scales (PRS): Measures both adaptive and problem behaviours in the community and home setting. Self-Report of Personality (SRP): Provides insight into a person's thoughts and feelings. Designed for individuals of ages 2 to 25 years.	Questionnaire completed by the parent (PRS) or by the patient (SRP).	Patients aged (years:months): • BASC-3 PRS-P (preschool): 2:0 to 5:11 • BASC-3 PRS-C (child) : 6:0 to 10:11 • BASC-3 SRP-C (child): 8:0 to 10:11 English speaking countries at every second NCA.	The parent rating scales (PRS) of the BASC-3 instrument are summarised by the following composite scores: • Behavioral Index composite score • Internalising Problems Composite • Externalising Problems Composite Which are derived from the following clinical and adaptive scales: hyperactivity, aggression, anxiety, depression, somatization, attention problems, atypicality, withdrawal, adaptive skills, adaptability, social skills, activities of daily living, functional communication, conduct problems (PRS-C) and leadership (PRS-C). The self-report of personality (SRP) of the BASC-3 instrument are summarised by the following composite scores: • Emotional Symptoms Index • School Problems Composite • Internalising Problems Composite • Inattention/Hyperactivity Composite Which are derived from the following clinical and adaptive scales: attitude to school, attitude to teachers, locus of control, social stress, anxiety, depression, sense of inadequacy, atypicality, personal adjustment, relations with parents, interpersonal relationships, self-esteem and self-reliance.

ABAS-3 Adaptive Behaviour Assessment System - Third Edition	Measure of adaptive behaviour, focused on home and community setting. This includes the ability to maintain independence and meet cultural expectations. Designed for individuals of ages 0 to 89 years.	Questionnaire completed by the parent.	Patients aged (years:months): - ABAS-3 Parent 0-5: 1:0 to 5:11 - ABAS-3 Parent 5-21: 6:0 to 10:11 English-speaking countries at every second NCA.	The ABAS-3 instrument is summarised by the <i>general adaptive composite score*</i> which is derived from the following adaptive domains and skill areas: Conceptual reasoning domain - Communication skill area - Functional pre-academics skill area/functional academics skill area - Self-direction skill area Social interactions domain - Leisure skill area - Social skill area Practical functioning domain - Community use skill area - Home living skill area - Health and safety skill area - Self-care skill area
BRIEF/BRIEF-2 Behaviour Rating Inventory of Executive Function.	Measure of executive function within the context of the patient's everyday environments. This includes systematic problem solving and task completion, self-regulation, regulation of emotional responses and the ability to adjust to changes in environment or plans. Designed for individuals aged 2 to 90 years.	Questionnaire completed by the parent.	Patients aged (years:months): - BRIEF-P (preschool): 2:0 to 5:11 - BRIEF-2 Parent: 6:0 to 10:11 All countries at every NCA.	The BRIEF instrument is summarised by the <i>global executive composite score (GEC)</i> which is derived from the following indices and clinical scales: BRIEF-P (preschool): Inhibitory self control index (ISCI) - Emotional control scale - Inhibit scale Flexibility index (FI) - Shift scale - Emotional control scale Emergent metacognition index (EMI) - Working memory scale - Plan/organize scale BRIEF-2 Parent: Behavioral regulation index (BRI) - Inhibit scale - Self-monitor scale Emotion regulation index (ERI) - Shift scale - Emotional control scale Cognitive regulation index (CRI) - Initiate scale - Task monitor scale - Working memory scale - Plan/organize scale - Organisation of materials scale
Cogstate custom battery	Measure of attention including processing speed and working memory, which has been identified as measures of cognitive impairment. The assessment involves reaction time test and visual recognition. Designed for individuals aged 4 to 21 years.	Computerised test completed by the patient	Patients aged (years:months): - Cogstate Paediatric Battery: 4:0 to 9:11 - Cogstate Adult Battery: 10:0 to 10:11 All countries at every NCA.	The Cogstate battery is summarised by the <i>attention domain composite score</i> which is derived from the following tests: Detection Identification One-Back (only for paediatric battery ages 6-9 and adult battery 10-21)

* Sometimes referred to as *Adaptive Behavior Domain*

Abbreviations: BASC-3 = Behaviour Assessment System for Children, Third Edition; BRIEF-2= Behaviour Rating Inventory of Executive Function, Second Edition; BRIEF-A = Behaviour Rating Inventory of Executive Function, Adult Edition; BRIEF-P =Behaviour Rating Inventory of Executive Function, Preschool Edition; NCA = neurocognitive assessment; PRS = parent rating scale; PRS-C = parent rating scales, child (PRS-C); PRS-P = parent rating scales, pre-school; WASI-II = Wechsler abbreviated scale of intelligence, 2nd edition; WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition

The following neurocognitive domains in this trial were assessed in all countries at every NCA:

☐ **Executive function:** The Global Executive Composite score is an overarching summary score that incorporates all of the Behaviour Rating Inventory of Executive Function ((BRIEF 2) clinical scales (Table 47) and report three indices:

☐ The Behaviour Regulation Index, which relates to systematic problem solving and, more generally, supports appropriate self-regulation

□ The Cognitive Regulation Index relates directly to the ability to actively problem solve in a variety of contexts and to complete tasks such as schoolwork.

□ The Emotion Regulation Index which represents the child's ability to regulate emotional responses and to shift set or adjust to changes in environment, people, plans, or demands.

Three (3) rating scales were used and these are described in Table 47.

□ Cognitive assessments (Attention/processing speed /working memory): The Cogstate computerised cognitive test battery completed by the patient and assessed the processing speed and attention by visual and verbal stimuli. Two (2) rating scales were used. Please refer to Table 47 for details.

Further, the following neurocognitive domains were assessed in English speaking countries at every second NCA:

□ General cognitive ability/intelligence was assessed by Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II) for patients aged 7 to 21 years which provides a full scale IQ composite score estimating intellectual functioning (Table 47).

□ Behavioural/emotional neurocognition: The behavioural assessment system for children-third edition (BASC-3) measures both emotional and behavioural problems by parents (PRS), and self-report (SRP). Five (5) rating scales were used. Please refer to Table 47 for more details. The composite scores for the BASC-3 are presented in Table 47.

□ Adaptive behaviour was assessed by the adaptive behaviour assessment system- third edition (ABAS-3). An Adaptive Behaviour Domain Score assessed level of everyday performance of tasks that is required for a person to fulfil typical roles in society. Two (2) rating scales were used. Please refer to Table 47 for further details.

Neurological and neurocognitive assessments were performed every 6 months and at least 6 days after the last dose at the end of trial visit in trial 3774 and according to the trial flowchart table 48 in trial 3895:

Table 48 Trial flowchart

Visit number	0 ¹⁵	1-20 ^{13, 15}	21-22	23	24-27	28	29-X ¹⁷	IFU	EOT
Visit purpose	Screening	Dosing	Dosing	End of Main	Dosing	End of extension	Dosing (until EOT)	ONLY for inhibitor patients	End of Trial
Time of visit (ED(s)) ¹⁹	0	1-20	30,40	50	60, 70, 80, 90	100	124, 148, 172, ...		
Visit interval ¹⁹		±1 Day	10 ± 2 weeks	10+2 Weeks	10 ± 2 weeks	10+2 weeks	24 ± 4 ¹⁷ weeks		
Neurological examination ²⁴		Visit 1 and 20		X	Visit 26	X	X		X
Neurocognitive assessments ²⁵		Visit 1 and 20		X	Visit 26	X	X		X

An independent EERP (External Expert Review Panel) evaluated key neurodevelopmental, neurocognitive, neurological and neurobehavioral milestones in Trials 3895 and 3774 on individual level and on trial level. The EERP consisted of neuropsychologists, a paediatric neurologist and a haematologist.

The neuropsychologists and paediatric neurologist of the EERP evaluated the results of the initial and subsequent neurocognitive and neurological assessments and provided individual narratives, including a categorisation of whether or not clinical concerns and contributing factors were identified for the patients. A clinical concern was defined as a cognitive performance or rating scale outcome below a

cut-off of -1.5 SD versus the eTHINK study (HAEM-4436, eTHINK study). A deterioration in all domains for a patient could also give rise to as a clinical concern, even though the cut-off of -1.5 SD was not reached. Contributing factors were identified from the patient's SDH and HH, and from other sources presenting factors which could impact cognitive or behavioural development. Most patients with a clinical concern had contributing factors. However, a patient could have a contributing factor (e.g. premature birth) but no clinical concern at first assessment. The EERP were not provided with information about dosing and did not evaluate the neurocognitive results in the light of treatment with nonacog beta pegol.

The EERP met every 6 to 12 months to evaluate information on all exposed patients with at least 1 NCA. A summary report from each EERP meeting was prepared by Cogstate Ltd. assisted by 2 EERP members acting as consultants. Based on the EERP evaluation, Novo Nordisk performed an overall evaluation of the theoretical risk associated with PEG exposure.

Neurological and neurocognitive data up until 25 November 2020 from Trials 3774 and 3895 are included in this summary.

Compiled summary of the EERP evaluation reports (Trials 3774 and 3895)

- ☐ Most patients were within normal limits for age-based neurocognitive performance measures and rating scales at initial assessment.
- ☐ No consistent pattern was observed for cognitive or behavioural performance for patients with or without clinical concern over time (change from initial to last assessment).
- ☐ The identified concerns were somewhat dependent on consistency of measures available for various age groups and at various timepoints. Thus, in the younger patients the primary identified concerns were in language and motor domains of which abnormal language was most frequent reported and often consistent with pre-existing neurological conditions such as language delay or ASD. In the older patients, the primary identified concerns were in attention, processing speed and executive functioning often consistent with pre-existing contributing factors.
- ☐ Most patients rated with 'normal' neurologic examinations at initial assessment remained stable at subsequent assessments.
- ☐ Four (4) out of 16 patients in Trial 3774 had clinical concerns at initial assessment, and 1 patient had a 'might be' clinical concern. Thirteen (13) out of 38 patients in Trial 3895 had clinical concerns at initial assessment. Most of these patients had significant contributing factors consistent with the neurocognitive findings. In the younger patients (Trial 3895), 5 out of the 13 patients with an initial clinical concern changed to having no clinical concern, and 2 (out of 13) changed to having a 'might be' clinical concern at subsequent assessment. In the older patients (Trial 3774), 2 out of the 4 patients with an initial clinical concern changed to having a 'might be' clinical concern, and the 1 patient with a 'might be' clinical concern at initial assessment changed to having no clinical concern at subsequent assessment.
- ☐ Out of the 11 patients with no clinical concern at initial assessment in Trial 3774, 1 patient changed to having a clinical concern at subsequent assessment. Out of 25 patients with no clinical concern at initial assessment in Trial 3895, 1 patient changed to having a clinical concern at subsequent assessment. These 2 patients had pre-existing contributing factors.
- ☐ Out of the 11 patients with no clinical concern at initial assessment in Trial 3774, 1 patient changed to having a 'might be' clinical concern at subsequent assessment. Out of the 25 patients with no clinical concern at initial assessment in Trial 3895, 3 patients changed to having a 'might be' clinical

concern at subsequent assessment. Two (2) of these 4 patients did not have contributing factors; however, questionable attention at repeated measures and inconsistent battery findings were observed for these patients.

Overall evaluation by Novo Nordisk of patients with clinical concern.

In both trials, most patients with clinical concerns had significant contributing factors consistent with, and considered to explain, the neurocognitive findings. The main contributing factors were developmental delay, family history of neurological or neurocognitive disorders, head injury and premature birth.

Approximately 40% of the younger patients with a clinical concern at initial assessment changed to having no clinical concern at subsequent assessment. These patients will not be discussed further.

A small fraction of patients did not have a clinical concern at initial assessment but changed to having a 'yes' or 'might be' clinical concern during the trial:

□ In Trial 3774, 1 patient developed a clinical concern during the trial. The patient had multiple contributing factors including macrosomia at birth, participation in contact sports, head injury, pre-existing attention problems and AE related to COVID-19 symptoms.

□ In Trial 3895, 1 patient developed a clinical concern during the trial. The patient had multiple contributing factors including pre-existing ICH, cerebral cyst and seizures and received antiseizure medication.

□ A total of 4 patient changed from having no clinical concern at initial assessment to a 'might be' clinical concern at subsequent assessment. The contributing factors reported for 2 of these patients were Tourette's syndrome or family history hereof, head injury/injuries, premature birth, and contact sports. For the remaining 2 patients, no contributing factors were reported, although one patient had initial parent-reported adaptive and language difficulties and the other patient had a head injury. Both patients had attention performance below clinical cut-off at latest assessments; one patient with questionable attention on repeated measures and the other patient with inconsistent batteries and mixed findings. Both patients had normal NEs, including normal language.

In conclusion, patients with clinical concern were represented in all instruments, in all age groups and across the entire exposure scale, and no consistent trend was observed for patients with high exposure versus patients with low exposure. The categorisation of a 'clinical concern' in Trials 3774 and 3895 was evaluated not to be related to nonacog beta pegol exposure.

Key conclusions from the latest EERP report (EERP meeting 3):

The latest EERP meeting (Meeting 3) was held on 13 January 2022 and 14 January 2022 during which data from trials 3774 and 3895 were reviewed with the data cut-off date of 15 October 2021. At this date, a total of 25 patients were screened and exposed to nonacog beta pegol for trial 3774 and 54 patients were screened and exposed to nonacog beta pegol for trial 3895. The latest EERP report included available neurocognitive data for 16 patients for trial 3774 and 41 patients for trial 3895.

Overall, the majority of patients evaluated were functioning within normal limits for age based on performance measures and rating scales at initial assessment. About half of the 15 patients identified at the initial visit to have clinical concerns were no longer identified as having clinical concerns by the most recent subsequent visit. The remaining patients continued to be identified as having a clinical concern, and more than half had contributing factors. While 3 patients did not have additional cognitive data at Meeting 3, the rest did and overall, the patterns were consistent, not worsening cognitive functioning in the areas the patients had initial deficits.

In summary, extensive evaluation of all safety data in the paediatric Trials 3774 and 3895 has not identified any safety issues related to PEG exposure:

- No pattern of cognitive or behavioural performance was detected by an independent EERP of neuropsychologists and a neurologist who evaluated key neurodevelopmental, neurocognitive, neurological and neurobehavioral milestones in the two trials on an ongoing basis, both at trial level and at individual patient level.
- No indications of any neurodevelopmental deficits caused by long-term exposure were found and patients in the paediatric Trials 7999-3774 and 7999-3895 had a performance comparable to a normative control group (eTHINK study).

Taking the rareness of haemophilia B and the limited available paediatric patient population into account, a total 72 paediatric patients have been exposed to nonacog beta pegol for up to more than 8 years which Novo Nordisk considers to be long-term exposure. Since December 2017 extensive safety measures and evaluations have been implemented to thoroughly evaluate and document potential effects of long-term exposure to nonacog beta pegol without identification of any safety issues related to PEG exposure in these paediatric patients. Further, the conclusion from the EERP meeting 3 is in line with the first 2 meetings or earlier reported data.

The MAH provided the requested EERP meeting outcomes dating from March 2023, as well as the evaluation of the previous meeting from March 2022. The most recent evaluations are consistent with the previous EERP reports and no new safety concern has emerged.

Safety related to drug-drug interactions and other interactions

No drug interaction studies have been performed and no interactions of nonacog beta pegol with other medicinal products have been reported.

Discontinuation due to adverse events

Adverse events leading to withdrawal

Trials in PTPs

Two (2) patients were withdrawn from the trials due to AEs (Table 49). One of the events was an allergic-type hypersensitivity reaction. The other case was a fatal event of hepatocellular carcinoma.

Table 49 Listing of adverse events leading to withdrawal - Trials 3639, 3747, 3773, 3775 and 3774 - safety analysis set

Patient number	Age at trial entry/Age at onset of event (years)	Preferred term	ED	Relationship ^a	Serious ^b	Severity	Outcome
Trial 3639							
	25/26	Hypersensitivity	1	Probable	Yes	Severe	Recovered
Trial 3775							
	41/43	Hepatocellular carcinoma	72	Unlikely	Yes	Severe	Fatal

ED: Exposure day

a: The relationship to trial product as judged by the investigator as either probable, possible or unlikely.

b: Denotes if the adverse event is serious or not (yes/no). For Trial 3774, data are included until 25Nov2020. No adverse events leading to withdrawal were reported in Trials 3747, 3773 or 3774.

Trial in PUPs

Five (5) patients were withdrawn from the trial due to AEs (Trial 3895-EXT, Table 50).

Table 50 Listing of adverse events leading to withdrawal – Trial 3895 - safety analysis set

	Age at trial entry/age at onset (years)	Preferred term	ED	Relationship ^a	Serious ^b	Severity	Outcome
	0/2	Hypersensitivity	10	Probable	No	Moderate	Recovered
	0/1	Factor IX inhibition	4	Possible	Yes	Moderate	Not recovered
	0/0	Haemorrhage intracranial	18	Unlikely	Yes	Severe	Fatal
	1/2	Language disorder	46	Possible	Yes	Moderate	Not recovered
	1/1	Anaphylactic reaction	4	Probable	Yes	Severe	Recovered
	1/1	Factor IX inhibition	4	Probable	Yes	Severe	Not recovered

ED: Exposure day

a: The relationship to trial product as judged by the investigator as either probable, possible or unlikely. b: Denotes if the adverse event is serious or not (yes/no).

The child with medical history of haemophilia B has reported "Language delay (chronic condition)" after receiving the trial product for one and a half years. Approximately 10 to 15 percent of two-year-old children have language delay, and 4 to 5 percent remain delayed after three years.

A large number of medical, and environmental conditions can cause or contribute to early language delays, particularly in the context of a more global developmental condition.

This patient has also been diagnosed with a suspicion of ADHD that needs to be followed up. Language disorders are often present in children with ADHD. The patient has a brother diagnosed with autism.

Based on the currently available information and prevalence in the background population, the sponsor evaluates the event to be unlikely related to the trial products and more likely to be related to ADHD and/or environmental factors.

Post marketing experience

Estimated market exposure

As of 31 May 2022, nonacog beta pegol with the trade name Refixia/Rebinyon has been approved worldwide for the treatment of haemophilia B in 44 countries (Table 51).

Table 51 Countries with marketing approval for nonacog beta pegol and approved indications

Country	Prophylaxis (40 IU/kg OW)	On demand (40 IU/kg)	Surgery (40-80 IU/kg)
Canada, United States, Switzerland, Japan, Argentina, Colombia, India, United Arab Emirates	All Ages	All Ages	All Ages
European Union, Serbia, North Macedonia, Lebanon, Taiwan, Australia, Saudi Arabia, Albania, United Kingdom (Great Britain)	≥ 12 Years	≥ 12 Years	≥ 12 Years

Abbreviation: OW = Once Weekly

In the US, nonacog beta pegol (Rebinyon) was approved in 2017 by the FDA for use in adults and children with haemophilia B for on-demand treatment and control of bleeding episodes and for perioperative management of bleeding. More recently, nonacog beta pegol was authorised for prophylaxis treatment in patients of all age groups in the US on 29 July 2022.

Novo Nordisk has released a total sales volume of 175,402,000 IU of nonacog beta pegol. This is the total volume of product distributed from Novo Nordisk to external customers (including samples) and does not necessarily reflect the actual use in patients.

Considering that nonacog beta pegol is used for both treatment of bleeding and as prophylaxis, an estimated defined daily dose (DDD) for nonacog beta pegol could be calculated based on a once-weekly prophylactic dose of 40 IU/kg in a 60 kg patient (a suggested average patient weight, reflective of treatment in children and adults), equal to a DDD of 343 IU/day.

Based on these assumptions, the patient exposure for nonacog beta pegol is estimated as PYE using the formula:

$$\text{PYE} = \frac{\text{Reported sales (IU)}}{\text{DDD} \left(\frac{\text{IU}}{\text{day}} \right) \times 365 \left(\frac{\text{days}}{\text{years}} \right)}$$

The estimated global market exposure based on this formula is shown in Table 52.

Table 52 Estimated market exposure to nonacog beta pegol

	EEA ^a , Switzerland and UK	Japan	US	Rest of World ^b	Total
PYE ^c	670	133	155	443	1,401

As the exposure is based on volume distributed to external customers and average daily usage rather than actual patient exposure, the numbers can be over- or underestimated.

^a The EEA consists of the member states of the EU and three countries of the EFTA (Iceland, Liechtenstein and Norway).

^b Currently the 'Rest of World' category only includes exposure in Australia and Canada

^c PYE is calculated as reported sales (IU) / DDD (IU/day/365 [days/year]).

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

As part of post-approval pharmacovigilance activities, Novo Nordisk has monitored AEs from all available sources (spontaneous and solicited) including

- ☐ spontaneously reported ARs
- ☐ events from market research programmes and patient support programmes
- ☐ AEs reported during the ongoing PASS 4031 (EU) and PMS Study 4404 (Japan).

As of 31 May 2022, 251 AEs were reported from post-marketing sources and 51 of these were serious. AEs were most frequently reported within the SOCs Injury, poisoning and procedural complications (including 9 AEs of off-label use), General disorders and administration site conditions, Investigations and Nervous system disorders. In most of the cases, limited information was available, and it is not known whether a patient experiencing the event was a PTP or PUP.

Analysis of adverse events by area of interest

FIX inhibitors

The NNMQ search of 'antibody FIX' identified 3 SAEs (Anti-FIX antibody increased and FIX inhibition) among the 251 AEs reported from post-marketing sources (Table 53).

This does not change the understanding of the already known risk of FIX inhibition with nonacog beta pegol.

Table 53 Adverse events from post-marketing sources related to antibodies based on NNMQ search of 'antibody FIX'

Preferred term	Non-serious	Serious
Anti-factor IX antibody increased	0	1
Factor IX inhibition	0	2

Allergic/hypersensitivity reactions

The narrow and broad NNMQ search 'allergic reactions' identified 3 SAEs (1 fatal respiratory failure, 1 dyspnoea and 1 anaphylactic reaction) and 17 non-serious AEs among the 251 AEs reported from post-marketing sources (Table 54). A male patient in his eighties with haemophilia B and haematoma died from respiratory failure 1 week after receiving his last dose of nonacog beta pegol. No information was available on medical history, concomitant medication, clinical course of events leading to death, autopsy report and any other investigational findings, precluding complete medical assessment of the case.

Table 54 Allergic reactions from post-marketing sources based on NNMQ search

Preferred term	Non-serious	Serious
Pruritus	4	0
Cough	2	0
Dyspnoea	1	1
Peripheral swelling	2	0
Urticaria	2	0
Anaphylactic reaction	0	1
Drug eruption	1	0
Erythema	1	0
Flushing	1	0
Pharyngeal swelling	1	0
Rash	1	0
Respiratory failure	0	1
Swelling	1	0

Thromboembolic events

The SMQ 'thromboembolic events' did not identify any events.

Medication errors

The SMQ 'medication error' (broad and narrow) identified 15 adverse events, all non-serious (Table 55).

Table 55 Medication errors from post-marketing sources based on SMQ search

Preferred Term	Non-serious	Serious
Product dose omission issue	4	0
Incorrect dose administered	2	0
Inappropriate schedule of product administration	1	0
Incorrect dosage administered	1	0
Incorrect route of product administration	1	0
Injury associated with device	1	0
Product appearance confusion	1	0
Product storage error	1	0
Product use complaint	1	0
Underdose	1	0
Wrong technique in product usage process	1	0

Injection site reactions

The NNMQ 'injection site reaction' identified 10 AEs, all non-serious (Table 56).

Table 56 Injection site reactions from post-marketing sources based on NNMQ search

Preferred Term	Non-serious	Serious
Injection site pain	2	0
Application site pain	1	0
Infusion site bruising	1	0
Infusion site discolouration	1	0
Infusion site pain	1	0
Infusion site swelling	1	0
Injection site erythema	1	0
Injection site haemorrhage	1	0
Injection site swelling	1	0

Rare events

There were 7 non-serious AEs and 5 SAEs reported using NNMQ 'rare events' (broad and narrow) (Table 57).

Table 57 Rare events from post-marketing sources based on NNMQ search

Preferred Term	Non-serious	Serious
Heart rate decreased	4	0
Heart rate increased	1	1
Anaphylactic reaction	0	1
Atrial fibrillation	0	1
Ocular icterus	1	0
Palpitations	1	0
Pancreatitis	0	1
Syncope	0	1

Adverse events related to the theoretical safety concern of PEG

Altogether, the SMQ searches 'acute renal failure' and 'drug-related hepatic disorders' and the NNMQ search 'CNS events' captured 3 SAEs (syncope, cerebral haemorrhage and dizziness) and 26 non-serious AEs among the 251 AEs reported from post-marketing sources (Table 58).

Headache (8 events), tremor (5 events), and dizziness (4 events) were the most frequently reported events, and all except one dizziness were non-serious. The remaining events were reported only once or twice, hence with no clustering of events.

Novo Nordisk evaluates that these 29 AEs reported from post-marketing sources, with nonacog beta pegol as suspected product, are unlikely to be clinical consequences of long-term exposure to PEG based on the available evidence. For some of the events, patients had a medical or family history that point to alternative aetiologies, while other events are considered unlikely to be caused by long-term exposure to PEG due to insufficient exposure time. In some cases, the limited information precludes a full medical assessment.

Table 58 Adverse events related to the theoretical safety concern of PEG (based on SMQ and NNMQ searches)

Preferred term	Non-serious	Serious
Headache	8	0
Tremor	5	0
Dizziness	3	1
Presyncope	2	0
Anxiety	1	0
Cerebellar haemorrhage	0	1
Head discomfort	1	0
Hyperaesthesia	1	0
Hypoaesthesia	1	0
Insomnia	1	0
Nervousness	1	0
Nightmare	1	0
Ocular icterus	1	0
Syncope	0	1

EU PASS (Study 4031)

Study 4031 is an ongoing non-interventional PASS conducted at the request of the EMA. The primary objective of the study is to investigate the safety of nonacog beta pegol in prophylaxis and during long-term routine use in patients with haemophilia B, see Study 4031 Protocol. This study was initiated in April 2019 and as of the interim 2 data cut-off date of 31 March 2022, 41 patients have completed Visit 1, 27 patients have completed Visit 2, 19 patients have completed Visit 3, 8 patients have completed Visit 4, 2 patients have completed Visit 5 and 1 patient had completed Visit 6 or Visit 7. No adverse drug reactions were reported during the study period and FIX inhibition, allergic reactions and thromboembolic events were not reported in any patients.

No adverse drug reactions were reported during the study period and FIX inhibition, allergic reactions and thromboembolic events were not reported in any patients.

A total of 13 AEs were reported in 7 patients; of which 3 AEs in 1 patient were non-treatment emergent. Two (2) AEs were serious (Gastric ulcer and Cholecystitis) and 1 AE was reported as an AESI (Headache). All events were mild or moderate except 1 treatment emergent AE which was reported as severe (Cholecystitis). Most events were reported as resolved, except 4 events of which 1 event (treatment emergent) was reported as recovered with sequelae and the 1 event (1 treatment emergent) was reported as resolving. None of the events were considered related to nonacog beta pegol by the physician.

The study includes a yearly NE comprising the following parameters: level of consciousness, cranial nerves, coordination and fine motor functioning, reflexes, sensory, gait, strength and tone. Twenty-four (24) patients have had baseline NEs performed at Visit 1, and 3 patients have had a second NE at Visit 2. Three (3) additional patients had only had the NE at Visit. Four (4) patients had abnormal neurological findings at Visit 1. Of these 4 patients, 1 patient had abnormal neurological findings which continued to Visits 2, 3 and 4 and another patient had abnormal neurological findings which continued to Visits 2 and 3.

Overall, the use of nonacog beta pegol during routine clinical practice for treatment of bleeding episodes, routine prophylaxis and prevention of bleeding during surgery appears safe and effective and is consistent with the data provided with the application for the market authorisation. This conclusion is based on data from 41 patients enrolled in the study. The mean treatment period per patient was 1 year (study 4031).

Japan post-marketing surveillance study (Study 4404)

Study 4404 is an ongoing non-interventional PMS study in Japan. The primary objective of the study is to assess the safety of nonacog beta pegol during long-term routine use in patients with haemophilia B. This study was initiated in August 2019, 26 patients had been enrolled in the study by 31 May 2022, and recruitment is ongoing.

As of 31 May 2022, 12 AEs have been reported in this study, of which 5 were SAEs (osteomyelitis, fall, subcapsular renal haematoma, spinal compression fracture and appendicitis) (Table 59). No safety concerns were identified.

Table 59 Adverse events in the post-marketing surveillance Study post-marketing sources

Preferred term	Non-serious	Serious
Pregnancy of partner	1	0
Appendicitis	0	1
Contusion	1	0
Fall	0	1
Feeling abnormal	1	0
Flushing	1	0
Nasopharyngitis	1	0
Osteomyelitis	0	1
Paternal exposure during pregnancy	1	0
Pregnancy of partner	1	0
Spinal compression fracture	0	1
Subcapsular renal haematoma	0	1
Urinary tract infection	1	0

2.5.1. Discussion on clinical 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, Refixia was not authorised in the whole paediatric population. In the submitted non-clinical studies with nonacog beta pegol, no treatment related vacuolation was observed. However, in non-clinical studies with PEG alone, cellular vacuolation due to accumulation of 40 kDa PEG in certain tissues (choroid plexus of brain, macrophages in the interstitium of the choroid plexus, red pulp of the spleen and mandibular and mesenteric lymph nodes) in monkeys and rats was observed at doses 200-500 fold higher (rats) or 200 fold higher (*Cynomolgus* monkey) than the PEG load resulting from the recommended clinical dose. Although no neurological symptoms (e.g., tremor) occurred in the clinical studies, the clinical trial programme was not prospectively designed to investigate possible clinical effects of PEG accumulation on the function of presumed main target organs and an accumulation of PEG with possible long-term consequences was expected to pose a conceivable risk. Potential unfavourable effects associated with the accumulation of PEG in the choroid plexus or other tissues or impairment of neural development likely would only become symptomatic after long-term exposure over several years, and clinical data was only available for a limited duration at the initial MA, with 48 patients having accrued ≥ 100 exposure days and 57 <100 EDs.

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

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

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

- PEG plasma concentration (in Trials 3747, 3775, 3774 and 3895).
- Neurological examination (NE) (in Trials 3774 and 3895).
- Neurocognitive assessments (NCAs) (in Trials 3774 and 3895).
- Collection of all CNS-related AEs and renal AEs as MESIs (in Trials 3774 and 3895)
- Determination of eGFR as a renal biomarker (in Trials 3774 and 3895).

Exposure

The MAH presented a comprehensive safety evaluation in PTPs for nonacog beta pegol which are considered supportive data.

In PTP trial 3774, 13 subjects 7-12 years of age and 12 subjects 0-6 years of age were enrolled and subjects have now accrued up to 436 EDs representing up to 8 years of treatment.

In PUP trial 3894, 50 subjects <6 years of age were enrolled and subjects have now accrued up to 324 EDs representing up to 6 years of treatment. The majority of subjects (62%) achieved > 100 EDs.

Following request, the MAH clarified the number and demography of PUP subjects in study 3895 starting “pre-prophylaxis” and prophylaxis, respectively. A substantial number of children <2 years of

age (i.e. n=17) was exposed to weekly prophylaxis, and in addition 34 subjects <1 year of age started with pre-prophylaxis, of whom 20 received prophylaxis with longer dosing intervals and not only on-demand treatment of bleeds. Therefore, a meaningful amount of clinical data in PUPs < 2 years of age, who have in the meantime accrued years of exposure is available to support the safety and efficacy of nonacog beta pegol in the youngest age groups.

Adverse Events

AE incidence

PTPs: The rate of AEs per patient year was 7.4 in children <6, 4.1 in children >6-12, 2.2 in adolescents and 2.7 in adults >18. The AE rate for children below 13 years of age was higher than in older PTPs in the PTs 'Infections and infestations' and 'Injury, poisoning and procedural complications'. In children below 6 yoa, the AE rate for the PT 'Respiratory, thoracic and mediastinal disorders', driven by cough, was higher as the comparable rate in the older age cohorts. These differences reflect the higher incidence of infections and respiratory disease as well as accidents in younger children.

PUPs: The AE rate in PUPs (5.21 AEs/ PYE) was comparable to that observed in PTPs <7 (7.4 AEs/ PYE) and PTPS <13 (4.1 AEs/ PYE).

Severe AEs

PTPs: The two severe AEs reported in one subject in the 0-<6 age group were viral upper respiratory tract infection and catheter site infection and were unlikely related to nonacog beta pegol as judged by the investigator, which is supported.

The hypersensitivity reaction described as a severe AE and considered related to nonacog beta pegol happened in trial 3639 (the FIH trial) and is already reflected in the EPAR.

PUPs: The 4 severe AEs assessed as possibly or probably related by the investigator were autism spectrum disorder in one patient, hypersensitivity in one patient and anaphylactic reaction and FIX inhibitor in one patient.

Related AEs

PTPs: In the age group 0-6 years, 2 AEs in one patient were assessed as related (abdominal pain, diarrhoea), and in the age group 6-12 years, 6 AEs in 3 patients were considered related to nonacog beta pegol (infusion /injection site pain, headache, nausea, eosinophilia).

The MAH was asked why the AEs of headache and eosinophilia, which were assessed as related, are not reflected in section 4.8 of the SmPC. The MAH has provided additional data and clarifications justifying that the abovementioned TEAEs are unlikely ADRs and therefore do not need to be reflected in the SmPC. This was agreed.

PUPs: 10 subjects reported 20 AEs that were assessed as related by the investigator, the majority of these AEs were immune reactions and development of inhibitors.

Most Frequently Reported AEs

PTPs: Upon request, the MAH summarised the most frequent AEs (reported in >10% of patients and >5% of patients) for the age cohorts 0-<6, 6-<12, total <12. In line with the safety profile observed in all treated patients irrespective of age, the most frequently reported AEs were in the SOC of injury, poisoning and procedural complications as well as infections and infestations.

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

Serious adverse events

Following request, the MAH provided data and narratives for all SAEs that occurred since the last database lock in Feb 2021 to the latest database lock in Oct 2022.

PTPs: All SAEs in children < 12 were assessed as unlikely related to nonacog beta pegol by the investigator which can be supported concluding from the nature of the SAE and/or the narratives, respectively. The SAEs in children <12 yoa encompassed infections (viral gastroenteritis, viral upper respiratory infection, catheter site infection), food poisoning, radius fracture and Tourettes syndrome.

The patient with Tourette syndrome was a 6y old boy enrolled in trial 3774. He started treatment with Refixia, displayed provisional and transient tics and was diagnosed with Tourette syndrome. The patient did not have any signs of ADHD, OCD or autism. The patient had tics and no other symptoms of Tourette. No family history of Tourette syndrome was described, however per his mother's statement, his mother's cousin also had tourette syndrome. The investigator and the sponsor both assessed the relationship to nonacog beta pegol as 'unlikely'. This evaluation is accepted.

PUPs: The related SAEs pertain to events of hypersensitivity and emergence of an inhibitor. Language disorder and ASD are also MESIs.

Deaths

One death was reported in a patient enrolled in the PUP trial 3895, which was caused by intracranial haemorrhages, which were likely aggravated due to the development of an inhibitor. The investigators assessment of relatedness of these 2 AEs (ICH- not related, inhibitor – possibly related) is accepted. In addition, since the latest cut-off, one death due to an ICH was reported In PUP trial 3895. The patient was a 19 month old male who received preprophylaxis. The last nonacog beta pegol infusions was given 8 months before the intracranial bleed. No relationship to Refixia is likely.

MESI

Following request, the MAH provided data and narratives for all MESIs that occurred since the last database lock in Feb 2021 to the latest database lock in Oct 2022.

Very few renal AEs were reported in the clinical investigation programme and no safety issue arises from the renal AE profile.

The eGFR values in studies 3774 and 3895 do not give rise to concern. Similarly, no safety issues arise from the evaluation of the observed hepatic adverse events.

The MAH could observe no correlation between number of exposure days, PEG plasma levels and incidence of CNS-related adverse events. Taking into account the influence of genetic predispositions as well as consequences of intracerebral bleeds and head trauma on neurocognitive and neurological findings, a facilitating effect of PEG exposure was not evident. The incidence of some NCA and NE findings after a small number of exposure days and the improvement of such AEs during ongoing treatment do not point to PEG as a factor of relevant influence on CNS-related adverse events.

For reference, of the subjects enrolled into the e-THINK study who have never been exposed to a pegylated coagulation factor, a total of 71 (13.9%) were diagnosed with ADHD and 15 (2.9%) patients were diagnosed with ASD. Neurodevelopmental disorders were reported in 2.7%, tics were reported in 4.1% and headaches were reported in 14.7% of the total population.

Immunogenicity

The observed incidence of inhibitors in PUPs is in line with recent literature reports of the inhibitor incidence in patients with severe haemophilia B (Male et al; Haematologica 2021, 106(1):123-129).

For three patients, information on the kind of F9 mutation was available, and all three displayed a nonsense mutation which confers a high inhibitor risk.

One subject in study 3774 developed anti-nonacog beta pegol antibodies without inhibitory effect. The patient tested negative for these antibodies at later visits and is continuing in the trial. One paediatric subjects from trial 3774 tested positive for anti-CHO antibodies at the end of the main phase and negative at subsequent visits.

In PUPs, anti-nonacog beta pegol antibodies arose simultaneously with FIX inhibitors in 4 patients, while the three other subject with such antibodies were only transiently positive or already positive before exposure to Refixia. Several patients were positive for anti-CHO antibodies, but without clinical consequences.

No specific concern arises with regard to immunogenicity in paediatric PUPs and PTPs.

PEG plasma levels

The measurable PEG plasma concentration reached a ceiling value after approximately 20 -30 weeks treatment with nonacog beta pegol. Mean values are comparable between PUPs and PTPs, with the older age cohort displaying slightly higher levels.

The clinical significance of these values is unknown at present, however, PEG levels were not correlated with CNS-related AEs.

Neurological, neurocognitive and neurobehavioural evaluation

Both clinical trial protocols were amended in order to investigate potentially PEG-related AEs of special interest (i.e. renal, hepatic and CNS-related adverse events), to evaluate PEG plasma levels and to examine a potential influence of the PEG moiety on neurological, neurocognitive and neurobehavioural development. In order to provide a relevant reference dataset, the eThink study enrolled 551 males below 22 years of age with any severity of haemophilia A and B and investigated neurologic, neurocognitive and neurobehavioural function using age appropriate, validated testing systems. This dataset is considered to provide a more appropriate comparison option than data derived from healthy children without haemophilia, as disease specific comorbidities like sequelae of bleeding events (e.g. intracranial bleedings, target joints, ...) are reflected in both datasets and hence a confounding effect of these occurrences on neurological or neurocognitive function is more likely to be avoided.

The neurologic examinations were performed by physicians, while the neurocognitive and neurobehavioural assessment was conducted by licensed psychologists or neuropsychologists with expertise in neuropsychology and/or child assessment. A comprehensive battery of assessments were used, e.g. the Bayley Scales Of Infant and Toddler Development or the Wechsler Abbreviated Scale of Intelligence. Identical assessments were then employed to investigate neurologic, neurocognitive and neurobehavioural parameters in the subjects of PTP study 3774 and PUP study 3895. An EERP evaluated key neurodevelopmental, neurocognitive, neurological and neurobehavioral milestones in Trials 3895 and 3774 on individual level and on trial level. The EERP consisted of neuropsychologists, a paediatric neurologist and a haematologist.

Neurological and neurocognitive assessment of paediatric subjects exposed for several years to nonacog beta pegol did not reveal a trend towards specific neurological or neurocognitive effects. Subjects in study 3774 accrued up to 400 ED, and subjects in trial 3895 accrued up to 300 ED, which is 6-8 times more than the 50 EDs required by the FIX guidance (EMA/CHMP/BPWP/144552/2009 rev. 2 Corr. 1).

Clinical concerns observed at baseline resolved during treatment with nonacog beta pegol, and while several concerns were newly observed throughout the treatment phase, there was no clustering of

symptoms and some of those concerns were mitigated or resolved at a later point in time without change to the prophylactic treatment regimen, thus rendering the influence of PEG on the observed events as unlikely.

Post-marketing data

Most patients using Refixia in the post-marketing setting were PTPs > 12 years. Post-marketing reports of the use of nonacog beta pegol in clinical practice do not raise additional safety concerns.

2.5.2. Conclusions on clinical safety

The MAH has submitted a comprehensive dossier investigating the safety of long-term treatment with nonacog beta pegol on paediatric PTPs and PUPs. Exposures up to 8 years for PTPs and up to 6 years for PUPs were achieved during the extension phases of the two relevant trials, 3774 in 25 PTPs and 3895 in 50 PUPs.

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

A comprehensive investigation of neurological, neurocognitive and neurobehavioural parameters of both PTP and PUP subjects 0-12 years old did not reveal a relevant influence of PEG on neurological development and function during long-term treatment with nonacog beta pegol.

In conclusion, the safety profile in paediatric subjects < 12 years of age did not differ in a relevant manner from that observed in older subjects treated with nonacog beta pegol. The number of exposed paediatric subjects surpasses guideline requirements and can be considered ample taking into account the rarity of the disease. The duration of exposure is exceptional and allows the assessment of the long-term safety profile, which appears benign. A substantial number of children <2 years of age (i.e. n=17) was exposed to weekly prophylaxis, and in addition 34 subjects <1 year of age started with pre-prophylaxis, of whom 20 received prophylaxis with longer dosing intervals and not only on-demand treatment of bleeds. Therefore, a meaningful amount of clinical data in PUPs < 2 years of age, who have in the meantime accrued years of exposure, is available to support the safety and efficacy of nonacog beta pegol in the youngest age groups.

The extension of indication to children below 12 years of age is approvable from a safety perspective.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version 5.2 with this application.

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

The PRAC considered that the risk management plan version 5.2 is acceptable.

The main proposed RMP changes were the following:

- Proposed Indication: Treatment and prophylaxis of bleeding in patients with haemophilia B

(congenital factor IX deficiency). Refixia can be used for all age groups.

- Data from non-clinical studies including the findings from juvenile neurotoxicity study in male rats has been updated.
- Data from clinical trials (including the 2 paediatric trials) and post-marketing sources (including exposure) and for epidemiology has been updated as of the DLP.
- Re-naming of the important potential risk "Accumulation of PEG in the brain (choroid plexus) and in other tissues/organs after long-term treatment" to "Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment' ".
- Inclusion of a new strength of 3000IU approved for treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency) based on positive opinion received on 13 Oct 2022 (EMA/H/C/004178/X/0027/G) via line extension procedure.

Safety concerns

Summary of safety concerns – nonacog beta pegol

Summary of safety concerns	
Important identified risks	• Allergic/hypersensitivity reactions • FIX inhibitors
Important potential risks	• Thromboembolic events • Nephrotic syndrome following ITI • Inadequate treatment due to assay overestimation of FIX activity • Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment
Missing information	• Females, including pregnant or breastfeeding women

Abbreviations: FIX = factor IX; ITI = immune tolerance induction; PEG = polyethylene glycol.

Pharmacovigilance plan

Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit risk)				
NN7999-4031 A non-interventional post-authorisation safety study (PASS) in male haemophilia B patients receiving nonacog beta pegol (N9-GP) prophylaxis treatment. Ongoing	Safety of nonacog beta pegol in prophylaxis during long-term routine use in patients with haemophilia B in the manner prescribed by the physicians.	• FIX inhibitors • Allergic/hypersensitivity reactions • Thromboembolic events • Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment	Interim results	First interim: When 5 patients have had their first visit after one year of inclusion. Second interim: When 25 patients have had their first visit after one year of inclusion.
			Study progress reports	As a PAM, the reports will be submitted yearly by 14 th December until the final study report submission.
			Submission of final results	Q2 2028 (planned study report finalisation: 07 Jun 2028)
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit-risk)				
None	N/A	N/A	N/A	N/A

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities (by the CHMP/PRAC or NCA)				
NN7999-4413 Non-interventional registry study (PASS) Adverse event data collection from external registries on nonacog beta pegol Ongoing	To investigate potential clinical effects of long-term exposure to nonacog beta pegol in patients with haemophilia B and to assess specific pharmacological risks for FIX replacement products including nonacog beta pegol.	• FIX inhibitors • Allergic/hypersensitivity reactions • Thromboembolic events • Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment	End of study	15 Dec 2027
			End of data collection	02 Feb 2028
			Reporting of study results	PSURs based on annual reports from registry
Clinical trial NN7999-3774 (phase 3a) Safety, efficacy and pharmacokinetics of nonacog beta pegol in previously treated children with haemophilia B Main phase completed. Extension phase ongoing	To evaluate immunogenicity of nonacog beta pegol in previously treated paediatric patients with haemophilia B	• FIX inhibitors • Allergic/hypersensitivity reactions • Thromboembolic events • Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment	Final CTR	22 May 2024 (planned)
Clinical trial NN7999-3895 (phase 3a) Safety and efficacy of nonacog beta pegol (N9-GP) in previously untreated patients with haemophilia B Main phase completed. Extension phase ongoing	• Incidence of inhibitory antibodies against FIX • Frequency of adverse events • Annualised bleeding rate • Haemostatic effect on treatment of bleeds	• FIX inhibitors • Allergic/Hypersensitivity reactions • Thromboembolic events • Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment	Final CTR	16 Apr 2023 (planned)

Abbreviations: CTR = clinical trial report; FIX = coagulation factor IX; N9-GP = nonacog beta pegol; N/A = not applicable; PAM = post-authorisation measure; PASS = post-authorisation safety study; PEG = polyethylene glycol.

Risk minimisation measures

Pharmacovigilance and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Allergic/hypersensitivity reactions	<i>Routine risk minimisation measures:</i> <u>Routine risk communication:</u> The identified risk of allergic/hypersensitivity reactions is addressed in the labelling: Section 4.8 of the SmPC and Section 4 of the PL. Hypersensitivity to the active substance or excipients and known allergy to hamster protein are listed as contraindication in Section 4.3 of the SmPC and Section 2 of the PL. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Information on how to detect early signs of allergic/hypersensitivity reactions is included in Section 4.4 of the SmPC and Section 2 of the PL. <u>Other routine risk minimisation measures beyond the Product Information:</u> None <i>Additional risk minimisation measures:</i> None	<i>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</i> Hypersensitivity questionnaire (Annex 4B) <i>Additional pharmacovigilance activities:</i> PASS (NN7999-4031) Clinical trial (NN7999-3774, NN7999-3895) PASS registry study (NN7999-4413)

FIX inhibitors	<i>Routine risk minimisation measures</i> <u>Routine risk communication:</u> The identified risk of FIX inhibitors is addressed in the labelling: Section 4.8 of the SmPC and Section 4 of the PL. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Recommendation for careful monitoring by appropriate clinical observations and laboratory tests included in SmPC Section 4.4 and PL Section 2. <u>Other routine risk minimisation measures beyond the Product Information:</u> None <i>Additional risk minimisation measures:</i> None	<i>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</i> FIX inhibitor questionnaire (Annex 4A) <i>Additional pharmacovigilance activities:</i> PASS (NN7999-4031) Clinical trial (NN7999-3774, NN7999-3895) PASS registry study (NN7999-4413)
Important potential risks		
Thromboembolic events	<i>Routine risk minimisation measures</i> <u>Routine risk communication:</u> The potential risk of thromboembolic events is addressed in the labelling: Section 4.8 of the SmPC and Section 2 of the PL. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> A recommendation is included in Section 4.4 of the SmPC to monitor for early signs of thrombotic and consumptive coagulopathy by appropriate clinical observations and appropriate biological testing in patients with liver disease, in patients post-operatively, in newborn infants, or in patients at risk of thrombotic phenomena or DIC. <u>Other risk minimisation measures beyond the Product Information:</u> None <i>Additional risk minimisation measures:</i> None	<i>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</i> Thromboembolic event questionnaires (Annex 4C) <i>Additional pharmacovigilance activities:</i> PASS (NN7999-4031) Clinical trial (NN7999-3774, NN7999-3895) PASS registry study (NN7999-4413)

Nephrotic syndrome following ITI	<i>Routine risk minimisation measures</i> <u>Routine risk communication:</u> The potential risk of nephrotic syndrome following ITI is addressed in the labelling: Section 4.8 of the SmPC and Section 2 of the PL. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None <u>Other risk minimisation measures beyond the Product Information:</u> None <i>Additional risk minimisation measures:</i> None	<i>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</i> None <i>Additional pharmacovigilance activities:</i> None
Inadequate treatment due to assay overestimation of FIX activity	<i>Routine risk minimisation measures</i> <u>Routine risk communication:</u> Section 4.2 of the SmPC includes information about the risk of FIX activity overestimation by use of a specific assay. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None <u>Other risk minimisation measures beyond the Product Information:</u> None <i>Additional risk minimisation measures:</i> None	<i>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</i> None <i>Additional pharmacovigilance activities:</i> None
Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment	<i>Routine risk communication:</i> None <i>Routine risk minimisation activities recommending specific clinical measures to address the risk:</i> None <i>Other risk minimisation measures beyond the Product Information:</i> None	<i>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</i> Targeted follow-up questions regarding hepatic and renal impairment and CNS-related adverse events (Annex 4D) Aggregated safety data analyses in PSURs <i>Additional pharmacovigilance activities:</i> PASS (NN7999-4031) Clinical trial (NN7999-3774, NN7999-3895) PASS registry study (NN7999-4413)

Missing information		
Females, including pregnant or breastfeeding women	<i>Routine risk minimisation measures</i> <u>Routine risk communication:</u> Lack of experience in this population is mentioned in Section 4.6 of the SmPC. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None <u>Other risk minimisation measures beyond the Product Information:</u> None <i>Additional risk minimisation measures:</i> None	<i>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</i> None <i>Additional pharmacovigilance activities:</i> None

Abbreviations: DIC = disseminated intravascular coagulation; FIX = factor IX; ITI = immune tolerance induction; PASS = post-authorisation safety study; PEG = polyethylene glycol; PL = package leaflet; rFIX = recombinant factor IX; SmPC = Summary of Product Characteristics.

There is no substantial change to the additional pharmacovigilance activities as of DLP of the current procedure, all activities are ongoing.

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

The proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The studies in the post-authorisation development plan are sufficient to monitor the effectiveness of the risk minimisation measures.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the MAH took the opportunity to introduce minor editorial changes to the PI. Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

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

The MAH referred to the already performed user consultation made for the marketing authorisation application approved in June 2017 and that only minor and no significant changes have been made.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Haemophilia B is an X-linked recessive congenital bleeding disorder, caused by mutations in the genes encoding coagulation factor IX (FIX), with an incidence of approximately one in every 25,000 male births.

Haemophilia B is often categorised according to residual FIX activity level. Patients with severe haemophilia B (FIX activity <1%) experience bleeds, particularly into joints and muscles, often without any apparent reason (spontaneous bleeds). In contrast, patients with mild haemophilia B (FIX activity of 5% to 40%) rarely experience spontaneous bleeds and bleeding in these patients is often caused by trauma or surgery.

3.1.2. Available therapies and unmet medical need

The World Federation of Hemophilia (WFH) recommend prophylaxis as the optimal therapy for patients with severe haemophilia and that patients begin prophylaxis prior to the onset of joint disease and ideally before 3 years of age. The most conservative Nordic Haemophilia Guidelines recommend starting prophylactic treatment at the age of 1 year before joint bleedings occur.

Current replacement therapy includes plasma-derived (pdFIX) as well as recombinant FIX (rFIX) products. These products are indicated for both the prophylactic and acute treatment of bleeding episodes, including bleeding in the perioperative setting. Half-life of both pdFIX and rFIX is ~18 hours. Prophylactic treatment with those products is usually required 2 to 3 times a week in order to achieve a significant reduction of bleeding episodes. Several years ago, FIX products with a prolonged half-life have been licensed, which can be given once per week or even less often.

3.1.3. Main clinical studies

The main evidence supporting the extension of indication in children (<12 years of age) with haemophilia B is based on the data from **PTP trial 3774** and **PUP trial 3895**. 25 paediatric PTPs (1-12 years old) were enrolled in trial 3774 and 50 paediatric PUPs (0-5 years old) were enrolled in trial 3895. PTPs received routine prophylaxis treatment of nonacog beta pegol 40 IU/kg once weekly, and PUPs could either enrol directly into prophylaxis at the same dose as PTPs or they could enter a pre-prophylaxis phase where they received nonacog beta pegol on demand or at intervals longer than once weekly.

3.2. Favourable effects

Mean steady state Factor IX trough levels, as estimated from pre-dose samples during prophylaxis with 40 IU/kg, were stable for up to 450 weeks after treatment initiation and within the range of mild haemophilia between 0.05 and 0.4 IU/mL (0.146 IU/mL and 0.195 IU/mL for patients 0-6 years and 7-12 years old, respectively). Similarly stable long-term steady state levels were also demonstrated for PUPs ≤6 years with an estimated mean of 0.156 IU/mL. Levels commonly achieved with unmodified FIX products are in the range of 0.01-0.03 IU/mL

The poisson-estimated ABRs were 1.02 (95%CI: 0.68; 1.54) and 0.84 (95%CI: 0.41; 1.75) in children ≤ 6 years and 7-12 years (median ABR 0.55 and 0.52), respectively, (data include up to 8 years of prophylaxis treatment). In PUPs ≤ 6 years the median ABR was 0.25 and the poisson-estimated ABR was 0.65 (95%CI: 0.34; 1.25). In support of the reported bleeding rate, a high proportion of subjects did not experience bleeding episodes during prophylaxis treatment (41.7% in PTPs ≤ 6 years, 30.4% in PTPs 7-12 years and 46.8% in PUPs ≤ 6 years throughout main and extension phases of trials 3774 and 3895).

Bleeding episodes were largely controlled by a single injection (82.9% for PTPs ≤ 6 years and 84.1% for PTPs 7-12 years) and the treatment response was mostly rated as good or excellent (88% and 93% for children ≤ 6 years and 7-12 years, respectively). Similarly, in PUPs 91.9% of breakthrough bleeds during prophylaxis treatment were treated with a single injection and 96.1% were rated as treatment success (i.e. good or excellent response). The median amount needed to treat a bleeding episode was around 43 IU/kg (42.2 IU/kg in PTPs ≤ 6 years, 43.2 IU/kg in PTPs 7-12 years and 44.2 IU/kg in PUPs ≤ 6 years). No target joint developed throughout the rather long observation period of both trials in PUPs and PTPs, whereas two pre-existing target joints in PTPs resolved.

3.3. Uncertainties and limitations about favourable effects

The haemostatic response evaluation for minor surgeries was not reported in trials 3774 (in PTPs ≤ 12 years) and 3895 (in PUPs ≤ 6 years). However major surgeries were conducted in two paediatric patients (one PTP and one PUP). The number of patient is small but excellent haemostatic response was reported for the treatment with 80 IU/kg.

No severe bleedings occurred in paediatric PTPs, which is a favourable outcome regarding prophylactic dosing, but leaves uncertainty regarding the recommended dosing (i.e. 80 IU/kg). Of the 7 severe bleeds that occurred in PUPs, 3 were successfully treated, 1 was rated as treatment failure and 3 were also treated with other Factor IX products or bypassing agents, which hampers interpretation of the response to nonacog beta pegol.

It is noted that all subjects included in trials 3774 and 3895 had severe (factor IX level $<1\%$) or moderately severe (factor IX level $\leq 2\%$) haemophilia B.

3.4. Unfavourable effects

Adverse Events

The observed adverse event profile in children below 12 years was comparable to that already shown in adolescents and adults, a higher AE rate was driven by infections and injuries, as can be expected for a young paediatric population. The AE profiles in PTPs and PUPs were similar.

Related Adverse Events

PTPs: In the age group 0-6 years, 2 AEs in one patient were assessed as related (abdominal pain, diarrhoea), and in the age group 6-12 years, 6 AEs in 3 patients were considered related to nonacog beta pegol (infusion /injection site pain, headache, nausea, eosinophilia).

PUPs: 10 subjects reported 20 AEs that were assessed as related by the investigator, the majority of these AEs were immune reactions and development of inhibitors.

Deaths

One death was reported in a patient enrolled in the PUP trial 3895, which was caused by intracranial haemorrhages, which were likely aggravated due to the development of an inhibitor. In addition, since the latest cut-off, one death due to an ICH was reported in PUP trial 3895. The patient was a young child who received preprophylaxis. The last nonacog beta pegol infusions was given 8 months before the intracranial bleed. No relationship to Refixia is likely.

The evaluation of immunogenicity and Medical Events of Special Interest (renal, hepatic, CNS-related AEs) did not reveal a safety signal.

Neurological, neurocognitive and neurobehavioural evaluation

Both clinical trial protocols were amended in order to investigate potentially PEG-related AEs of special interest (i.e. renal, hepatic and CNS-related adverse events), to evaluate PEG plasma levels and to examine a potential influence of the PEG moiety on neurological, neurocognitive and neurobehavioural development. In order to provide a relevant reference dataset, the eThink study enrolled 551 males below 22 years of age with haemophilia A and B and investigated neurologic, neurocognitive and neurobehavioural function using age appropriate, validated testing systems. The neurologic examinations were performed by physicians, while the neurocognitive and neurobehavioural assessment was conducted by licensed psychologists or neuropsychologists with expertise in neuropsychology and/or child assessment. A comprehensive battery of assessments were used, e.g. the Bayley Scales Of Infant and Toddler Development or the Wechsler Abbreviated Scale of Intelligence. Identical assessments were then employed to investigate neurologic, neurocognitive and neurobehavioural parameters in the subjects of PTP study 3774 and PUP study 3895. An External Expert Review Panel evaluated key neurodevelopmental, neurocognitive, neurological and neurobehavioral milestones in Trials 3895 and 3774 on individual level and on trial level. The EERP consisted of neuropsychologists, a paediatric neurologist and a haematologist.

Neurological and neurocognitive assessment of paediatric subjects exposed for several years to nonacog beta pegol did not reveal a trend towards specific neurological or neurocognitive effects. Subjects in study 3774 accrued up to 400 ED, and subjects in trial 3895 accrued up to 300 ED, which translates into 8 and 6 years of treatment with nonacog beta pegol, respectively.

Clinical concerns observed at baseline resolved during treatment with nonacog beta pegol, and while several concerns were newly observed throughout the treatment phase, there was no clustering of symptoms and some of those concerns were mitigated or resolved at a later point in time without change to the prophylactic treatment regimen. This renders an influence of PEG on the observed events as unlikely.

Post-marketing data

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

3.5. Uncertainties and limitations about unfavourable effects

The number of exposed paediatric subjects is numerically small but surpasses FIX guideline requirements and can be considered ample taking into account the rarity of the disease. The duration of exposure is very long for a FIX clinical investigation programme and allows the assessment of the long-term safety profile.

The MAH has extensively investigated pathways by which PEG metabolism could influence clinical outcomes, i.e. renal, hepatic and CNS-related adverse events. Furthermore, comprehensive

neurological, neurocognitive and neurobehavioural assessment consecutively over several years in all exposed PTPs and PUPs <12 years of age did not reveal appreciable differences to the paediatric haemophilia population of the eTHINK study, who was never exposed to a pegylated coagulation factor.

To supplement the clinical outcomes with results of tissue and CSF analyses, a juvenile animal neurotoxicity study was conducted to evaluate the potential neurotoxicity of nonacog beta pegol and especially the PEG moiety after i.v. administration of 120-1200 IU/kg/twice weekly (corresponding to a 1-10-fold clinical PEG plasma exposure) to juvenile male rats from D21 to D91, followed by a 13-week recovery period. As expected, PEG was found widely distributed to various tissues in a dose- and time-dependent manner, including choroid plexus and neuronal structures. However, alterations on neurobehavioral and neurocognitive development or other neuropathological changes were not observed in juvenile animals. PEG was below LLOQ in the cerebrospinal fluid (CSF) at all time points tested and IHC stainings confirmed that PEG was not passing the blood-brain barrier in nonacog beta pegol treated animals. Vacuole formation in the choroid plexus, a common uncertainty previously associated with PEG exposure, was observed in both, the treatment as well as control animals at similar levels, thus neither considered adverse nor treatment-related. Thus, as already shown in adult rats and monkey in the original MA, no PEG related vacuolation was observed in the juvenile rats' choroid plexus.

No new data on PEG alone treatment, which was shown to induce cellular vacuolation due to accumulation of 40 kDa PEG in certain tissues (including choroid plexus of brain, macrophages in the interstitium of the choroid plexus, red pulp of the spleen and mandibular and mesenteric lymph nodes) in adult monkeys and rats in the original MA, were submitted. However, these findings were observed at doses 200-500 fold higher than the PEG levels resulting from the recommended clinical dose, without any adverse (neurological) effects observed in these animals. Although the human relevance of PEG alone treatment at such high supraclinical exposure levels is questionable, it was concluded that due to the uncertainties around this issue and missing data in juvenile animals and children, use of nonacog beta pegol in the paediatric population at all ages, was not conceivable at that time.

The data submitted in juvenile animals treated with nonacog beta pegol revealed only slight accumulation in macrophages in the pituitary gland, which was considered to represent a normal physiological processing of foreign material in that cell type. However, at PEG exposure levels showing acceptable safety margins compared to clinical dosing, no other adverse findings were observed that would indicate an increased risk of PEG accumulation in juvenile rats. To note, the nonclinical studies provided do not allow a definite conclusion to be drawn on the risk for children aged less than 2 years since the juvenile studies provided do not cover this period (rats treated from 3 to 13 weeks of age corresponding to 2 to 16 years of age in humans). However, 41 PUPs <2 and 3 PTPs <2 years were exposed to (pre-) prophylaxis with nonacog beta pegol, the precise duration and dose of exposure are requested to be clarified by the MAH.

A dedicated animal model to investigate long-term consequences of potential PEG accumulation in (juvenile) animals is still not available, however the provided nonclinical data in juvenile rats focussing on neurologic development appears reassuring and supports the newly provided clinical data in the target population, which obviously constitutes the most important increase in knowledge, compared to the original MA.

3.6. Effects Table

Table: Effects Table for Refixia

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Factor IX activity	Long-term steady state trough levels	IU/mL	40 IU/kg weekly	N/A	Mean trough levels PTPs 0-6 years: 0.146 IU/mL (95% CI: 0.127; 0.167) PTPs 7-12 years: 0.195 IU/mL (95% CI: 0.172; 0.22) PUPs ≤6 years: 0.156 IU/mL (95% CI: 0.144; 0.170) Support for stable Factor IX levels in paediatric haemophilia B patients	Studies 3774 and 3895 - Main and extension phases
Annualised bleeding rate	Breakthrough bleeding episodes during prophylaxis		40 IU/kg weekly	N/A	PTPs 0-6 years: 1.02 (95% CI: 0.68; 1.54) PTPs 7-12 years: 0.84 (95% CI: 0.41; 1.75) PUPs ≤6 years: 0.65 (95% CI: 0.34; 1.25) Support for prophylaxis dosing	Studies 3774 and 3895 - Main and extension phases
Haemostatic response	Treatment of breakthrough bleeding events	Treatment success/failure	40 IU/kg on demand	N/A	Treatment success PTPs 0-6 years: 88% PTPs 7-12 years: 93% PUPs ≤6 years: 96.4% Support for on demand dosing	Studies 3774 and 3895 - Main and extension phases
Unfavourable Effects						
Related AEs				N/A		
PTPs	8/613 AEs					
	abdominal pain		1			
	diarrhoea		1			
	nausea		1			
	infusion site		1			

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	pain					
	injection site pain		1			
	eosinophilia		1			
	headache		1			
	wheezing		1			
PUPs	20/741 AEs			N/A		
	Hypersensitivity, Anaphylaxis		5			
	Inhibitors		4			
	Rash		4			
	Infusion site extravasation		1			
	Pyrexia		1			
	Hypoacusis		1			
	Conjunktivitis		1			
	Accidental underdose		1			
	Language disorder		1			
	Autism spectrum disorder		1			
<i>AE of special interest</i>				N/A		
Inhibitor			4 PUPs			
Anaphylaxis			1 PUP			
Thrombo-embolic events			2 in 1 PTP			
Renal AEs			2 PTPs >12yoa			
Hepatic AEs			1 in 1 PTPs, 1 PUP		All unlikely related	
CNS-related AEs			52 in 30 PTPs (PTPs of any age)		5 related (5 AE of headache in 5 PTPs, 2 AE of speech disorder in 1 PUP)	
			35 in 15 PUPs		2 related (1 AE of ASD in 1 PUP, 1 AE of language delay in 1 PUP)	

Abbreviations: AE... adverse event; PTP...previously treated patient; PUP...previously untreated patient

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Favourable and stable Factor IX levels for a long treatment duration (i.e. within the range of mild haemophilia for up to 450 weeks) were further substantiated by low bleeding rates in paediatric patients. Thus, it is concluded that the proposed treatment with 40 IU/kg provides an efficacious prophylaxis option for paediatric haemophilia B patients (PTPs and PUPs). Furthermore, breakthrough bleeding events required mostly only a single injection in order to achieve good or excellent treatment response.

The observed safety profile in children below 12 years of age was comparable to the safety profile already established in adolescents and adults. The long-term safety profile in children (up to 8 years exposure in PTPs and up to 6 years in PUPs) did not reveal any unusual safety signals. A comprehensive neurological, neurocognitive and neurobehavioural assessment in PTP trial 3774 and PUP trial 3895 demonstrated neurological function and development parameters comparable to the dataset provided by the 551 haemophiliac subjects of the eThink study, who had never been exposed to a pegylated coagulation factor. Furthermore, renal and hepatic parameters did not suggest a detrimental effect caused by long-term PEG exposure. Overall, comprehensive investigations of potential risks associated with PEG exposure were done, even exceeding recommendations given in previous SA. Postmarketing data, although mainly derived in PTPs ≥ 12 years of age, do not give rise to concern with regards to potential PEG-related adverse events.

Clinical data are supported by outcomes from a juvenile animal neurotoxicity study in male rats, where exposure to nonacog beta pegol with a safety margin of corresponding to 1-10 times the clinical PEG plasma exposure did not lead to adverse events, including signs of neurotoxic or adverse neurobehavioral development. The newly provided nonclinical data on PEG exposure in juvenile animals together with the nonclinical data of the original MA thus support treatment with nonacog beta pegol in all age groups from a nonclinical perspective.

3.7.2. Balance of benefits and risks

The beneficial effects of prophylaxis and treatment with nonacog beta pegol in children < 12 years of age pertain to a low annualised bleeding rate preserved over several years of prophylaxis achieved with a once weekly infusion interval. The trough levels both in PTPs as well as in PUPs show values consistent with the category of mild haemophilia, which is likely to translate into a protective effect against spontaneous bleeding events and the development of target joints. This assumption is supported by the development of zero target joints in PUPs and the resolution of two pre-existing target joints in PTPs with no new target joints observed throughout the whole study period (up to 8 and 6 years in PTPs and PUPs, respectively). The haemostatic efficacy was demonstrated in the treatment of bleeds and was satisfactory after one infusion in the vast majority of BEs.

The long-term safety profile was benign with no new safety signals compared to the safety profile in adolescents and adults. The rate of inhibitor development in PUPs was consistent with such rates reported in the literature. Comprehensive neurological, neurocognitive and neurobehavioural assessments throughout both studies did not reveal a noticeable influence of nonacog beta pegol on neurological function and development.

In conclusion, the demonstrated beneficial effects of treatment with nonacog beta pegol with regard to sustained low ABRs and trough levels in the range of mild haemophilia at a once weekly infusion interval as well as a satisfactory haemostatic efficacy combined with a benign long-term safety profile,

new long-term data that were collected prospectively and specifically investigating potential PEG-related effects together with additional nonclinical data support the use in both paediatric PTPs below 12 years as well as in PUPs.

3.8. Conclusions

The overall B/R of Refixia for the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency) is positive.

4. Recommendations

Outcome

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

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

Extension of indication to include treatment and prophylaxis of bleeding in children below 12 years of age with haemophilia B including previously untreated patients for Refixia based on results from studies NN7999-3774 and NN7999-3895. NN7999-3774 is a multicentre, open-label, non-controlled study evaluating the safety, efficacy and pharmacokinetics of nonacog beta pegol in previously treated children with haemophilia B, while NN7999-3895 is a multicentre, open-label, single-arm, non-controlled trial evaluating the safety and efficacy of nonacog beta pegol in previously untreated patients with haemophilia B. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated accordingly. Version 5.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI. The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

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

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0139/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Refixia is not similar to Idelvion, Alprolix nor Hemgenix within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Refixia-H-C-004178-II-0032'