EMA/125435/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Esperoct

International non-proprietary name: turoctocog alfa pegol

Procedure No. EMEA/H/C/004883/0000

Note

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

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	23 May 2022	23 May 2022	☐
☐	CHMP Rapporteur Assessment Report	27 Jun 2022	27 Jun 2022	☐
☐	CHMP members comments	11 Jul 2022	11 Jul 2022	☐
☐	Updated CHMP Rapporteur Assessment Report	14 Jul 2022	14 Jul 2022	☐
☐	Opinion/RSI	21 Jul 2022	21 Jul 2022	☐
☐	MAH submission of Responses	20 Sep 2022	20 Sep 2022	
☐	Re-Start of procedure	21 Sep 2022	21 Sep 2022	☐
☐	CHMP Rapporteur Assessment Report	28 Sep 2022	28.09.2022	☐
☐	CHMP members comments	03 Oct 2022	03 Oct 2022	☐
☐	Updated CHMP Rapporteur Assessment Report	06 Oct 2022	N/A	☐
☐	Request for Supplementary Information	13 Oct 2022	13 Oct 2022	☐
☐	Submission Deadline	15 Nov 2022	11 Nov 2022	☐
☐	Re-Start of procedure	16 Nov 2022	16 Nov 2022	☐
☐	CHMP Rapporteur Assessment Report	30 Nov 2022	30 Nov 2022	☐
☐	CHMP members comments	05 Dec 2022	07 Dec 2022	☐
☐	Updated CHMP Rapporteur Assessment Report	08 Dec 2022	07 Dec 2022	☐
☐	Request for Supplementary Information	15 Dec 2022	15 Dec 2022	☐
☐	Submission Deadline	24 Jan 2023	24 Jan 2023	☐
☐	Re-Start of procedure	25 Jan 2023	25 Jan 2023	☐
☐	CHMP Rapporteur Assessment Report	8 Feb 2023	8 Feb 2023	☐
☐	CHMP members comments	13 Feb 2023	13 Feb 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	16 Feb 2023	16 Feb 2023	☐
☒	Opinion	23 Feb 2023	23 Feb 2023	☐

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novo Nordisk A/S submitted to the European Medicines Agency on 2 May 2022 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of section 4.2 of the SmPC in order to delete the statement in reference to previously untreated patients (PUPs) and section 5.1 of the SmPC in order to update information based on final results from study NN7088-3908; this is an open-label single-arm multicentre non-controlled phase 3a trial investigating safety and efficacy of turoctocog alfa pegol (N8-GP) in prophylaxis and treatment of bleeding episodes in previously untreated paediatric patients with severe haemophilia A. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

The requested variation proposed amendments to the Summary of Product Characteristics.

Information on paediatric requirements

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

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

The PDCO issued an opinion on compliance for the PIP P/0142/2017.

2. Overall conclusion and impact on the benefit/risk balance

Turoctocog alfa pegol (referred as N8-GP or Esperoct here after) is a long-acting recombinant coagulation factor VIII (rFVIII) product, which is used for the treatment and prevention of bleeds in patients with haemophilia A. An extended half-life is achieved via the covalent conjugation of a 40 kDa (kilo Dalton) polyethylene glycol (PEG) moiety to an O-linked glycan site on the B-domain of turoctocog alfa. The mechanism of action for N8-GP is based on replacement of the deficient or absent FVIII in patients with haemophilia A.

Esperoct was approved by the CHMP (date of issue of marketing authorisation valid throughout the European Union: 20/06/2019) after a positive benefit-risk balance was concluded for subjects >12 years of age. However, the medicine is under additional monitoring. A PASS is ongoing to evaluate the long-term safety with respect to FVIII inhibitor development, allergic/hypersensitivity reactions and long term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs. Potential effects on brain development were also a crucial factor to conclude a negative benefit-risk for subjects <12 years. The ongoing long-term safety observation as well as the negative benefit-risk for subjects <12 years are not part of the requested changes as part of this type II variation.

The data presented for this type II variation address the clinical evidence for the treatment of previously untreated children (below 6 years) with severe haemophilia A. For this purpose the MAH presents an open-label study (trial 3908) to provide clinical evidence for previously untreated patients (PUPs) with haemophilia A that were treated with Esperoct following a pre-prophylactic (treatment of bleeds) and/or prophylactic (prevention of bleeds) treatment regimens. Data from this trial are intended to justify

revisions for the product information. More specifically the MAH intends to delete a statement regarding lack of data for PUPs in section 4.2 of the SmPC and to introduce a new chapter on study results in PUPs in section 5.1 of the SmPC.

As per guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009 rev. 2) formal PUP studies are not required but every PUP should be closely monitored with regards to treatment performance and inhibitor development. The availability of clinical data for PUPs provides product-specific information regarding the risk for developing anti-FVIII antibodies and is acknowledged. PUPs are of high risk to develop inhibitory antibodies (ABs) against FVIII. Inhibitors occur very commonly in PUPs with haemophilia A, usually within the first 50 exposure days. Thus, the chosen primary endpoint addressing the development of FVIII inhibitors is supported. In total 81 PUPs were exposed to Esperoct (a mean of 205.8 EDs per patient) and 49 subjects completed trial 3908 with the submission at hand (55 subjects started in pre-prophylaxis and 26 started in prophylaxis). As per GL regarding previously treated patients (PTPs), at least 25 patients should be <6 years who have undergone >50 EDs with previous factor VIII products. Patient numbers and EDs presented here for PUPs appear sufficient to principally conclude on efficacy and safety in PUPs.

During study 3908 26.25% of PUPs developed inhibitory antibodies against FVIII (21 of 80 patients) and 13.75% of subjects developed high titre inhibitory antibodies against FVIII (11 of 80 patients). Thus, incidence of FVIII inhibitor formation for Esperoct in PUPs is very common (i.e. frequency $\geqslant$1/10 patients), but is an expected frequency (as per outcome of the FVIII referral and FVIII Core SmPC) and appears comparable to other recombinant FVIII products (see Calvez et al 2014). Furthermore, the majority of FVIII inhibitors developed before ED50, which is in line with the expected highest risk during the first 50 EDs as depicted in the GL (EMA/CHMP/BPWP/144533/2009 rev. 2). Data on FVIII inhibitors in PUPs and PTPs are reflected in the SmPC section 4.8 (see also SmPC).

The occurrence of AEs was comparable to the incidence rates as reported for previously treated patients of the same age group (<6 years) in the current EPAR (96.3% and 94.1% of patients, respectively). However, the rate of serious AEs appears much higher for PUPs (59.3% and 29.4% of patients, respectively) and more PUPs had severs AEs (28.4% and 20.6% of patients, respectively). The MAH clarified that the higher rate of SAEs in PUPs can be attributed to the high rate of inhibitor-related SAEs in PUPs compared to the PTPs and the lower median age of the PUPs from trial 3908 (8 months) compared to the PTPs from trial 3885 (3 years) of the same age group (<6 years).

Presented results from study 3908 regarding efficacy in PUPs appear principally comparable to results as presented in the current EPAR for the treatment of previously treated patients of the same age group. Thus, no concerns arise from presented results on efficacy for trial 3908.

Regarding pharmacokinetics in PUPs treated with Esperoct, 17 patients were observed with consecutive low incremental recoveries (IRs) and further 14 patients had a single measure of low IR, whereas 28 subjects did not have any measure of decreased IR. These numbers indicate that the majority of the PUPs had at least one measure of a decreased IR. Based on a root-cause analysis the MAH concludes that a transient increase in anti-PEG antibodies is driving the transient decrease in IR for some PUPs. Due to low patient numbers, the analyses are not fully conclusive, but anti-drug antibodies appear to be a reasonable explanation for the observed drop in IR in some PUPs. The highest proportion of subjects with consecutive low IR had confirmed antibodies after exposure to Esperoct (64.7% had anti-N8-GP antibodies, 100% had anti-PEG IgG antibodies and 70.1% had anti-PEG IgM antibodies) and most of the subjects with low IR did not have antibodies at baseline, but developed such after exposure to Esperoct (58.8% for anti-N8-GP, 58.8% for anti-PEG IgG and 47.1% for anti-PEG IgM antibodies). Upon request, the MAH clarified that no PTPs were observed with consecutive low IR during trials 3859 and 3885. Also no decrease in IR was observed in paediatric PTPs with pre-existing anti-PEG antibodies at baseline. Thus, the correlation of anti-PEG antibodies and transient low IR appears conclusive only for PUPs. The

information on potentially reduced IR is an important identified risk that is considered clinically very relevant and should be reflected in the SmPC (section 4.4) once a label update is submitted to extend the indication to PUPs <6 years. As patients <12 years are currently not licensed for the treatment with Esperoct, it appears sufficient to include a respective statement regarding transient low IR in section 5.1 (as per SmPC guideline rev. 2).

In summary, the proposed change in 4.2 (i.e. deletion of the statement "The safety and efficacy of Esperoct in previously untreated patients have not yet been established") is acceptable based on provided data from trial 3908. Further information on PUPs is included in sections 4.8 and 5.1 of the SmPC.

The benefit-risk balance of Esperoct, remains positive for subjects >12 years of age. The benefit-risk remains negative for subjects <12 years of age, as depicted in the current EPAR. It is suggested that an update of the EPAR according to the results presented for PUPs will be initiated.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIB

Update of section 4.2 of the SmPC in order to delete the statement in reference to previously untreated patients (PUPs) and section 5.1 of the SmPC in order to update information based on final results from study NN7088-3908; this is an open-label single-arm multicentre non-controlled phase 3a trial investigating safety and efficacy of turoctocog alfa pegol (N8-GP) in prophylaxis and treatment of bleeding episodes in previously untreated paediatric patients with severe haemophilia A. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

☒ is approvable

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

Amendments to the marketing authorisation

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

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Submission of the final results from study NN7088-3908 which is an open-label single-arm multicentre non-controlled phase 3a trial investigating safety and efficacy of turoctocog alfa pegol in prophylaxis and treatment of bleeding episodes in previously untreated paediatric patients with severe haemophilia AUpdate of Section 4.2 to remove the statement. Section 4.2 and 5.1 have been updated accordingly. In addition, information on Factor VIII inhibition as "very common" event in PUPs is included in section 4.8 of the SmPC.

Amendments are requested. For more information, please refer to the SmPC.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Turoctocog alfa pegol (referred as N8-GP or Esperoct here after) is a long-acting recombinant coagulation factor VIII (rFVIII) product, which is used for the treatment and prevention of bleeds in patients with haemophilia A. The extended half-life is due to the covalent conjugation of a 40 kDa (kilo Dalton) polyethylene glycol (PEG) moiety to an O-linked glycan site on the B-domain of turoctocog alfa. The mechanism of action for N8-GP is based on replacement of the deficient or absent FVIII in patients with haemophilia A.

As of December 2021, N8-GP has received regulatory approvals in more than 35 countries worldwide, including the EEA, and is currently marketed under the trade name Esperoct. Esperoct was approved by the CHMP (Date of issue of marketing authorisation valid throughout the European Union: 20/06/2019) after a positive benefit-risk balance was concluded for subjects >12 years of age. However, the medicine is under additional monitoring. A PASS is ongoing to evaluate the long-term safety with respect to FVIII inhibitor development, allergic/hypersensitivity reactions and long term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs. The data presented for this type II variation from clinical trial 3908 address the clinical evidence for the treatment of previously untreated children (below 6 years) with severe haemophilia A utilizing Esperoct.

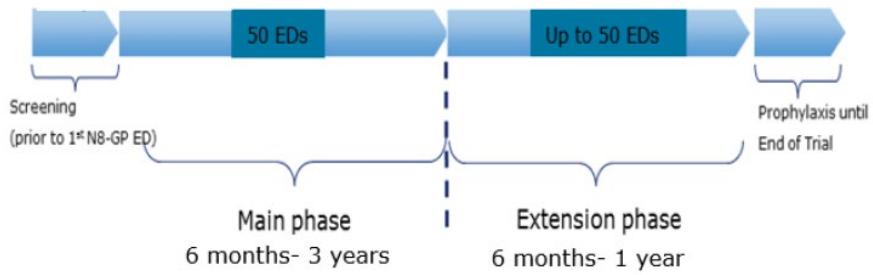
6. Clinical Efficacy aspects

6.1. Methods – analysis of data submitted

Trial 3908 was a multicentre, open label, non-controlled, single-arm trial that investigated safety and efficacy of N8-GP in prophylaxis and treatment of breakthrough bleeds in PUPs with severe haemophilia A (FVIII activity ≤1%). A pre-prophylaxis period up to 20 EDs or 24 months was optional, before initiation of prophylaxis treatment.

Trial 3908 consisted of the 6-month to 3-year main phase followed by a 6-month to 1-year extension phase. The main phase included both the pre-prophylaxis and prophylaxis treatment where patients received treatment with N8-GP until they reached a minimum of 50 EDs. During the extension phase, patients continued the prophylaxis dosing regimen until they reached a minimum of 50 EDs. The trial also consisted of a prophylaxis period until the end of the trial.

Figure 1: Trial Design



Abbreviations: ED = exposure days.

Primary Objective

To evaluate immunogenicity of N8-GP in previously untreated patients (PUPs) with severe haemophilia A.

The **primary endpoint** is a safety endpoint defined as incidence of inhibitory antibodies against FVIII.

Secondary Objectives

To evaluate safety other than immunogenicity of N8-GP in PUPs with severe haemophilia A

To evaluate efficacy of N8-GP in PUPs with severe haemophilia A

- in long-term prophylaxis treatment (bleeding preventive effect)

- in the treatment of bleeding episodes

There are no confirmatory secondary endpoints in this trial. **Supportive secondary endpoints** include "Number of bleeding episodes during prophylaxis (annualised)", "Haemostatic effect (4-point response scale: excellent, good, moderate and none)", "Incidence of confirmed high titre inhibitors (>5BU)", "FVIII consumption (for prophylaxis, for treatment of bleeding episodes, total per patient)", "Adverse events including SAEs and MESI", "Incremental recovery (IR30min)", "FVIII activity at 30 minutes (C30min)" and "FVIII trough level".

Changes in trial conduct

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

Table 1: Amendments to protocol

Amendment number	Issue date	Timing of change	Countries affected	Key changes
1	Not finalised	NA	Portugal	The protocol amendment was dedicated to Portugal but was never finalised. Due to SOP requirements the countries were required to have their own logs which would only cover global amendments
2	20 March 2015	After FPFV	Global	Detailed information on major surgery and ITI, extended trial timelines
3	01 November 2016	After FPFV	Global	This protocol amendment included a new secondary endpoint to assess the ITI treatment outcome and included monitoring of antibody development against Host Cell Protein (HCP).
4	14 June 2018	After FPFV	Israel	This protocol amendment was for Israel seeking permission to obtain the F8 genotype.
5	13 June 2019	After FPFV	Global	This protocol amendment specified interim analysis when approximately 45 patients had reached 50 EDs each, and additional administrative changes
6	21 June 2019	After FPFV	Israel	This protocol amendment for Israel was to obtain informed consent from withdrawn patients to provide genotype results
7	02 July 2019	After FPFV	Japan	This protocol amendment for Japan was due to that the regulatory category of this clinical trial should be updated in accordance with Japanese regulations. This was mandatory before NNPL could obtain marketing approval of N8-GP.
8	15 June 2020	After FPFV	Global	This protocol amendment specified the closure of recruitment to the trial, and that more than 50 but less than 100 patients would complete the trial. LPLV date 13 November 2021 was kept. Due to the observations of non-inhibitor patients with low IR, anti-PEG IgG and additional IgM antibody analyses were added to the assessments.

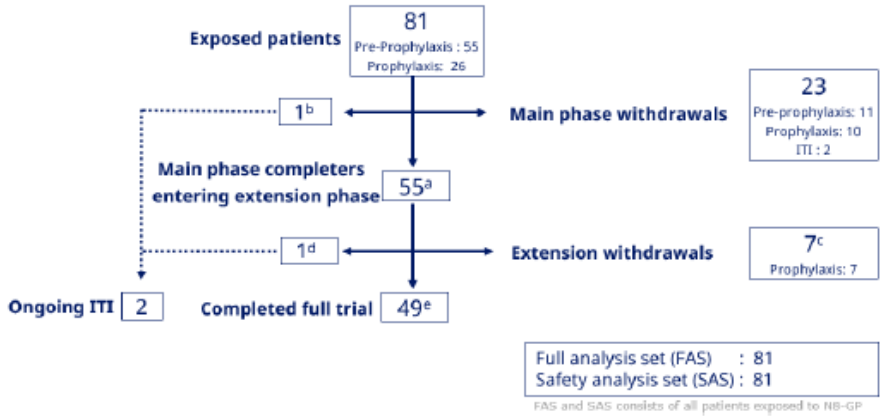
6.2. Results

6.2.1. Study conduct

Patient flow

A total of 88 patients were screened for participation in the trial, of which 82 patients were enrolled and 81 patients were exposed to N8-GP (one patient signed the informed consent but was not exposed). Of the 81 patients exposed to N8-GP, 55 patients started on pre-prophylaxis and 26 patients started on prophylaxis when entering the trial.

Figure 2: Schematic overview of patient flow during the trial



Abbreviations: ITI = immune tolerance induction; ED = extension phase

[a] Two (2) patients in the main phase were considered as trial completers due to early site closures (sit, but were not considered as main phase completers.

[b] One (1) patient started ITI without completing main phase and still ongoing.

[c] From 7 patients who withdrew during the extension phase, 3 patients completed 100 EDs but withdrew from the trial and were thus extension phase completers while 4 patients withdrew without completing extension phase.

[d] One (1) patient started ITI in extension phase and still ongoing. This patient also completed 100 EDs in the trial, hence is considered as an extension phase completer and is included in the 49 patients.

[e] Two (2) patients in the extension phase were considered as trial completers due to early site closures, but not as extension phase completer.

During the main phase, 42 patients switched from pre-prophylaxis to prophylaxis and 2 patients switched from pre-prophylaxis to ITI treatment. Patients who switched treatment regimen are represented in all 3 treatment regimen groups (pre-prophylaxis, prophylaxis, and total) where they contributed with data from the relevant treatment period.

Table 2: Patient disposition – all patients

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

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

Demographics and baseline characteristics

Table 3: Baseline demographics

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

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

Exposure

Table 4: N8-GP exposure – main + extension

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

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

Protocol deviations

Table 5: Summary of site and subject level important protocol deviations

Protocol deviation category	PD-type	Site level PDs N	Subject level PDs N	Total site and subject level PDs N
ASSESSMENT DEVIATIONS (INCL. LAB)	PD IMP	1	51	52
INCL./EXCL./RAND. CRITERIA	PD IMP	0	2	2
INCLUSION/EXCLUSION CRITERIA	DIA PD IMP	1	0	1
INFORMED CONSENT	DIA PD IMP	0	13	13
INFORMED CONSENT	PD IMP	4	9	13
SAE NOTIFICATION/SAFETY PROCEDURE	DIA PD IMP	3	2	5
SUBJECT VISIT SCHEDULE	DIA PD IMP	0	1	1
TREATMENT ADMINISTRATION	DIA PD IMP	2	9	11
TREATMENT COMPLIANCE	PD IMP	1	32	33
TRIAL PROCEDURES/ASSESSMENT	DIA PD IMP	5	26	31
TRIAL PRODUCT HANDLING	PD IMP	2	21	23
OTHER	PD IMP	5	34	39
Total		24	200	224

N: number of PDs within category, not allocated: PDs for screening failures and subjects not allocated to treatment.
DIA: Drug Information Association; IMP: Important; PD: protocol deviation; SAE: serious adverse event.

6.2.2. Efficacy and PK Results

Table 6: Detail of bleeds – main + extension

	Pre-prophylaxis	Prophylaxis	Total
Number of patients	55	69	81
Number of patients with bleed, N(%)	48 (87.3)	60 (87.0)	75 (92.6)
Number of bleeds	163	347	510
Cause of bleed, N (%)			
N	163 (100.0)	347 (100.0)	510 (100.0)
Spontaneous	56 (34.36)	64 (18.44)	120 (23.53)
Traumatic	104 (63.80)	280 (80.69)	384 (75.29)
Surgical	2 (1.23)	3 (0.86)	5 (0.98)
NK	1 (0.61)	-	1 (0.20)
Re-bleed*, N (%)			
N	163 (100.0)	347 (100.0)	510 (100.0)
Yes	-	1 (0.29)	1 (0.20)
No	163 (100.0)	346 (99.71)	509 (99.80)
Location of bleed, N (%)			
N	163 (100.0)	347 (100.0)	510 (100.0)
Joint	30 (18.40)	64 (18.44)	94 (18.43)
Muscular	17 (10.43)	43 (12.39)	60 (11.76)
Skin	76 (46.63)	146 (42.07)	222 (43.53)
Stomach/Gut (Blood in stool)	2 (1.23)	-	2 (0.39)
Mouth, Gums or Nose	23 (14.11)	55 (15.85)	78 (15.29)
CNS	1 (0.61)	6 (1.73)	7 (1.37)
Other	14 (8.59)	33 (9.51)	47 (9.22)
Severity of bleed, N (%)			
N	163 (100.0)	347 (100.0)	510 (100.0)
Mild/Moderate	156 (95.71)	338 (97.41)	494 (96.86)
Severe	4 (2.45)	9 (2.59)	13 (2.55)
NK	1 (0.61)	-	1 (0.20)
Missing	2 (1.23)	-	2 (0.39)
Location of bleed for severe bleeds, N (%)			
N	4 (100.0)	9 (100.0)	13 (100.0)
Joint	1 (25.00)	2 (22.22)	3 (23.08)
Skin	2 (50.00)	1 (11.11)	3 (23.08)
Mouth, Gums or Nose	-	3 (33.33)	3 (23.08)
CNS	-	2 (22.22)	2 (15.38)
Other	1 (25.00)	1 (11.11)	2 (15.38)
Time of onset of bleed, N (%)			
N	110 (100.0)	321 (100.0)	431 (100.0)
From 3 a.m. to 7 a.m.	1 (0.91)	10 (3.12)	11 (2.55)
From 7 a.m. to < 11 a.m.	40 (36.36)	79 (24.61)	119 (27.61)
From 11 a.m. to < 3 p.m.	20 (18.18)	53 (16.51)	73 (16.94)
From 3 p.m. to < 7 p.m.	22 (20.00)	98 (30.53)	120 (27.84)
From 7 p.m. to < 11 p.m.	25 (22.73)	72 (22.43)	97 (22.51)
From 11 p.m. to 3 a.m.	2 (1.82)	9 (2.80)	11 (2.55)
Time since last dose*, N (%)			
N	163 (100.0)	347 (100.0)	510 (100.0)
<=4 days	14 (8.59)	191 (55.04)	205 (40.20)
>4 days	81 (49.69)	125 (36.02)	206 (40.39)
Missing	68 (41.72)	31 (8.93)	99 (19.41)

Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns, with data from the relevant period.
Only primary location is summarised.
*Only calculated if start time of bleed is reported.
NK: not known

Table 7: ABR – main + extension

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

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

Table 8: Haemostatic response – main + extension

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

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

Haemostatic effect of N8-GP during surgery

A successful haemostatic effect was reported for 25 (83.3%) of the 30 minor surgeries (including missing responses considered as failures). A successful haemostatic effect was reported for 4 (100.0%) of the 4 major surgeries. Hence, a successful haemostatic effect was reported for 29 (85.3%) of the total 34 surgeries. The mean number of N8-GP doses per surgery was 4.5 (range: 1; 16), with a median of 3.0 number of doses per surgery.

Consumption of N8-GP for prophylaxis

The mean (SD) and median number of N8-GP doses used for prophylaxis per patient during main+extension phase was 236.6 (208.2) and 177 doses, respectively, ranging from 7 doses (in a withdrawn patient) to 792 doses per patient. A total of 15,762 prophylaxis doses were administered. The actual mean (SD) and median prophylaxis dose was 68.9 (7.6) and 69.0 IU/kg, respectively. This was within the per-protocol specified dose range of 50-75 IU/kg.

Consumption of N8-GP for treatment of bleeds

For the total 505 bleeds treated with N8-GP in 75 patients the mean number of injections per bleed was 1.4 (range: 1; 12), with a median of 1.0 number of injections per bleed. Of the 505 bleeds, 405 bleeds (80.2%) were treated with 1 injection and 55 bleeds (10.9%) were treated with 2 injections; hence 460 bleeds (91.1%) were treated with ≤2 injections of N8-GP. The mean (SD) and median total amount of N8-GP (IU/kg) used for treatment of a bleed was 98.6 (87.5) and 71.4 IU/kg per bleed, respectively.

There were no clinically significant differences between patients on pre-prophylaxis and prophylaxis with regards to number of injections and dose (IU/kg) of N8-GP used per bleed.

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

The mean annual consumption of N8-GP per patient (including all doses, i.e., for pre-prophylaxis, prophylaxis, treatment of bleeds, surgery, and PK assessments) was 4525.7 IU/kg/patient/year. The median annual consumption was 4027.0 IU/kg/year/patient with a range from 450.9 to 9083.4 IU/kg/year/patient.

Immune tolerance induction (ITI) treatment

Patients who developed FVIII inhibitors in the trial were offered ITI treatment with N8-GP. If a newly diagnosed inhibitor patient still responded well to treatment with N8-GP, initiation of ITI could be postponed with up to 6 months, or ITI could be cancelled if the inhibitors had resolved during the 6 months. If an inhibitor patient on ITI was confirmed negative for inhibitors (<0.6 BU), FVIII recovery should be measured after an injection of 60 IU/kg of N8-GP without washout period. If IR was shown to be ≥1.2 (IU/dL)/(IU/kg), a FVIII half-life assessment was to be conducted after injection of 60 IU/kg of N8-GP (after a 72 hours treatment-free washout period), and repeated if necessary, until the half-life was confirmed to be ≥9 hours.

A total of 21 patients developed FVIII inhibitors, of which 8 patients had initiated ITI treatment. Of the 8 patients who initiated ITI treatment, 6 patients had completed ITI treatment at the DBL, and 4 patients out of these had been reported by the investigator with a 'yes' to a clinical effect from ITI treatment. The status of 2 patients on ITI is still ongoing at the time of this report. Of the 13 inhibitor patients that had

not initiated ITI treatment during the trial, 11 patients had withdrawn from the trial while 2 patients received prophylaxis. Eight (8) bleeds were observed in 4 of the 8 ITI patients during ITI treatment. The ABR estimate (negative binomial model) was 0.84 (95% CI: 0.42; 1.68) bleeds/patient/year. The median ABR was 0.25 (interquartile range: 0.00; 1.32) bleeds/patient/year. Two (2) bleeds were treated with excellent haemostatic response, 3 bleeds were treated with good haemostatic response, and 3 bleeds were treated with moderate haemostatic response. The success rate for treatment of bleeds during ITI was 75.0% (95% CI: 23.8; 96.6). During ITI there were no MESIs, and there were 3 SAEs (all unlikely related to trial product and resolved/recovered).

Pharmacokinetic assessments – FVIII activity

Mean FVIII activity (IU/mL) at pre-dose and at 30 min post-dose, obtained with the chromogenic assay with PSS as calibrator, is presented by visit in Figure 11-1 for patients on twice weekly or every 3rd day prophylaxis regimen. FVIII activities in pre-dose samples (i.e., FVIII trough levels) were as expected due to the relatively high clearance of N8-GP in young children.

Figure 3: Profiles of mean FVIII activity (IU/mL) at pre-dose and at 30min post-dose by visit – chromogenic assay with PSS as calibrator – main + extension

The FVIII activity 30 min post dosing at visit 3, which corresponds to 5 EDs, was lower than expected for some patients. This observation is discussed in detail in the following Section. It should be noted that post-dose samples were not available for all patients at the early visits, and that later visits, from visits 7 and on, included more samples compared to the early visits.

Observations of decreased incremental recovery (IR)

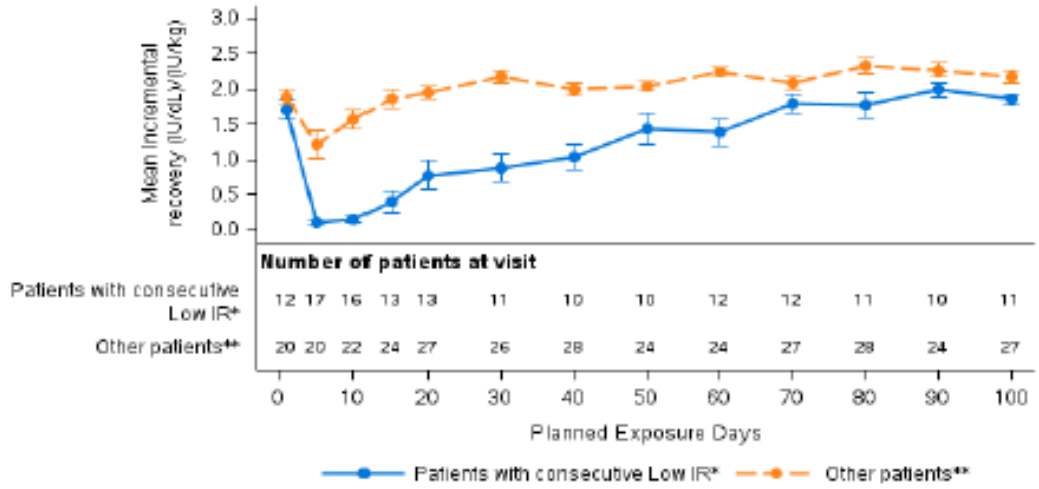
A safety signal related to observations of a decrease in incremental recovery (IR) following the initial administrations of N8-GP in the absence of detectable FVIII inhibitors in a proportion of PUPs was

observed in the trial. The safety signal was later evaluated by the Novo Nordisk safety committee to be an important identified risk of "low initial incremental recovery in PUPs".

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

A post hoc analysis of all available IR values obtained at baseline (the very first exposure; ED 1) to N8-GP in the present trial (N=45) has subsequently shown that the mean IR at first exposure to N8-GP was 1.76 (IU/dL)/(IU/kg) and the 5% percentile was 0.71 (IU/dL)/(IU/kg). Thus, based on the actual distribution of baseline IR, theoretically only 5% of all such values would fall below 0.71 (IU/dL)/(IU/kg). This supports that use of <0.6 (IU/dL)/(IU/kg) is a valid set point for definition of a decreased IR value, as was just defined above.

Figure 4: Profiles of IR (mean±SEM) (IU/dL)/(IU/kg) for patients with consecutive decreased IR (n=17) and "other" (n=42) non-inhibitor patients – chrom PSS



From Visit 1 to Visit 14.

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

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

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

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

Non-inhibitor patients with no measurements of decreased IR (N=28 patients): These patients had no decreased IR measurements (i.e., no observations of IR <0.6 (IU/dL)/(IU/kg)). Patients with missing measurements of IR were included, as were patients who withdrew before 10 EDs. Non-inhibitor patients with single measurement(s) of decreased IR (N= 14 patients): These patients had one single observation of decreased IR, but no consecutive observations of decreased IR. Non-inhibitor patients with consecutive decreased IR (N=17 patients): These patients have at least 2 consecutive observations of decreased IR.

A period of decreased IR in a patient was defined as the period from the last visit before the patient had the first decreased IR measurement until IR was again ≥0.6 (IU/dL)/(IU/kg).

Table 9: Details of bleeds occurring during periods of consecutive or single decreased IR in non-inhibitor patients, and for all bleeds in all patients during the trial – main + extension

	During consecutive decreased IR period Non-inhibitor patients	During single decreased IR period Non-inhibitor patients	All bleeds in trial All patients
Number of patients	17	14	81
Number of patients with bleed, N(%)	14 (82.4)	8 (57.1)	75 (92.6)
Number of bleeds	38	21	510
Cause of bleed, N (%)			
N	38 (100.0)	21 (100.0)	510 (100.0)
Spontaneous	9 (23.68)	6 (28.57)	120 (23.53)
Traumatic	27 (71.05)	15 (71.43)	384 (75.29)
Surgical	2 (5.26)	-	5 (0.98)
Location of bleed, N (%)			
N	38 (100.0)	21 (100.0)	510 (100.0)
Joint	8 (21.05)	1 (4.76)	94 (18.43)
Muscular	6 (15.79)	4 (19.05)	60 (11.76)
Skin	18 (47.37)	14 (66.67)	222 (43.53)
Stomach/Gut (Blood in stool)	-	-	2 (0.39)
Mouth, Gums or Nose	5 (13.16)	1 (4.76)	78 (15.29)
CNS	-	-	7 (1.37)
Other	1 (2.63)	1 (4.76)	47 (9.22)
Severity of bleed, N (%)			
N	38 (100.0)	21 (100.0)	510 (100.0)
Mild/Moderate	33 (86.84)	21 (100.0)	494 (96.86)
Severe	5 (13.16)	-	13 (2.55)
NK	-	-	1 (0.20)
Missing	-	-	2 (0.39)
Location of bleed for severed bleeds, N (%)			
N	5 (100.0)	-	13 (100.0)
Joint	2 (40.00)	-	3 (23.08)
Skin	1 (20.00)	-	3 (23.08)
Mouth, Gums or Nose	2 (40.00)	-	3 (23.08)
CNS	-	-	2 (15.38)
Other	-	-	2 (15.38)

Only primary location is summarised.
NK: not known.
Non-inhibitor patients correspond to those subjects identified as inhibitor negative before starting and during the trial.

Root cause analysis

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

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

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

Table 10: Mixed model incremental recovery vs. titre – non-inhibitor patients

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

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

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

6.3. Discussion

The MAH presents an open-label study to provide clinical evidence for PUPs with haemophilia A that were treated with Esperoct following a pre-prophylactic (treatment of bleeds) and/or prophylactic (prevention of bleeds) regimen. Initially it was planned that the analysis and evaluation for the main trial report will be performed when at least 50 patients have reached a minimum of 50 EDs each in the main phase and at least 100 patients have reached at least 100 EDs each before the trial is completed. However, a protocol amendment was conducted to introduce an interim analysis and in the scope of another protocol amendment the number of subjects required to complete the trial was reduced, due to upcoming recruitment issues. This amendment specified that initially planned patient numbers may not be met (i.e. 100 PUPs complete the trial) and that only a minimum of 50 PUPs would be required to complete the trial. In the end 81 PUP were exposed to Esperoct (a mean of 205.8 EDs per patient) and 49 subjects completed trial 3908 with the submission at hand (55 subjects started in pre-prophylaxis and 26 started in prophylaxis). No formal sample size calculations have been performed. Thus, no impact of reduced patient numbers on statistical considerations is expected. As per GL regarding previously treated patients, at least 25 patients should be <6 years. Thus, patient numbers and EDs presented here for PUPs appear sufficient to principally conclude on efficacy and safety in PUPs.

The development of FVIII inhibitors was chosen as primary endpoint of trial 3908, which is supported as anti-drug antibodies are a major concern for PUPs. Further details regarding the primary endpoint are being discussed in section 7. Clinical Safety Aspects. The selection of secondary endpoints for the evaluation of efficacy are in line with other FVIII products and fully supported. In summary, presented results from study 3908 regarding efficacy in PUP appear principally comparable to results as presented in the current EPAR for the treatment of previously treated patients of the same age group (i.e. <6 years; e.g. mean ABR of 3.1 and 3.46 (during prophylaxis), success/failure rate of 87/13% and 89/11%, mean prophylaxis dose of 65.3 IU//kg and 68.9 IU/kg in previously treated (as per study 3885 main + extension phase in EPAR) and previously untreated (as per study 3908 main + extension phase) subjects <6 years, respectively. Thus, no concerns arise from presented results on efficacy for trial 3908.

Data on immune tolerance induction (ITI) have been collected in PUPs with haemophilia A who have developed inhibitors to FVIII during trial 3908. However, patient numbers are not sufficient to draw any robust conclusions regarding the effect of ITI in PUP with anti-FVIII inhibitors during the therapy with Esperoct (n=8 PUP with FVIII-inhibitors started ITI, n=6 patients completed the ITI phase and n=4 had a positive clinical effect).

Regarding pharmacokinetics in PUPs treated with Esperoct, 17 patients were observed with consecutive low IRs and further 14 patients had a single measure of low IR, whereas 28 subjects did not have any measure of decreased IR. These numbers indicate that the majority of the PUP had at least one measure of a decreased IR. It is agreed with the MAH that "*a low IR could constitute a clinical concern in a patient*

as it indicates that the availability of the drug product in the blood is reduced". In line with this concern, bleeds in subjects with consecutive low IRs were more likely to be severe bleeds compared to the bleeds in all patients (13.2% and 2.5% of bleeds were severe, respectively) and the haemostatic response during periods of consecutive low IRs appears worse compared to the overall response for all bleeds (i.e. less excellent and more failed or moderate responses as well as a lower success rate). Furthermore, the proportion of subjects reporting an AE in the SOC Blood and lymphatic system disorders is more than 8-times higher in subjects with consecutive low IRs compared to all other patients (all other patients include those with a single event of low IR; 41.2% and 4.8%, respectively). Similarly, the SOC Reproductive system and breast disorders had higher rates in subjects with consecutive low IRs compared to all other patients (17.6% and 2.4%, respectively). Thus, clinical consequences in relation to the low IR were observed in study 3908, but it should also be noted that results are produced from *post-hoc* analyses and are compromised by low patient numbers. Importantly, the MAH provided a root-cause analysis from which the association to anti-drug antibodies (including PEG-IgG, PEG-IgM and anit-N8-GP) appears plausible. The observation of low IR for a subset of PUPs also triggered a protocol amendment to include further assessments of anti-PEG-IgG and anti-PEG-IgM antibodies. Based on further analyses, the MAH concludes that a transient increase in anti-PEG antibodies for some PUPs is driving the transient decrease in IR for these subjects. The biggest proportion of subjects with consecutive low IR had confirmed antibodies after exposure to Esperoct (64.7% of PUPs with consecutive low IR had anti-N8-GP antibodies, 100% had anti-PEG IgG antibodies and 70.1% had anti-PEG IgM antibodies) and most of the subjects with low IR did not have antibodies at baseline, but developed such after exposure to Esperoct (58.8% of PUPs with consecutive low IR had anti-N8-GP, 58.8% had anti-PEG IgG and 47.1% had anti-PEG IgM antibodies after exposure, but not at baseline). Due to low patient numbers, the analyses are not fully conclusive, but anti-drug antibodies appear to be a reasonable explanation for the observed drop in IR in some PUPs. It should be mentioned that the reduced IR was seen after the initial administrations of Esperoct and was transient as also seems to hold for the anti-PEG IgG antibodies. Taken together, the information on potentially reduced IR is an important identified risk that is considered clinically very relevant. Thus, findings on decreased IRs in a subset of PUPs should be adequately reflected in the EPAR. As patients <12 years are currently not licensed for the treatment with Esperoct, a statement regarding transient low IR in section 5.1 appears sufficient (as per SmPC guideline rev. 2). However, it is noted that a respective warning should be reflected in the SmPC (section 4.4) once a label update is submitted to extend the indication to PUPs <6 years. Additionally, closer monitoring of FVIII levels upon treatment initiation with this pegylated FVIII product in PUPs should be evaluated in more detail once licensure for paediatric subjects is requested. Upon request, the MAH amended the provided information on PUPs in section 5.1 of the SmPC.

7. Clinical Safety aspects

7.1. Methods – analysis of data submitted

Primary endpoint – Incidence of FVIII inhibitors

The primary endpoint of the trial was incidence of FVIII inhibitors. Assessment for the presence of inhibitors was mandatory at each clinical visit, and could also be performed at any time point at the discretion of the investigator. In case of a positive inhibitor test (≥0.6 BU), a second blood sample and a confirmatory inhibitor test was to be performed. If the second confirmatory test was positive, the patient was considered an inhibitor patient. Inhibitors >5 BU were defined as high titre inhibitors. An inhibitor patient counted only once (numerator) in the statistical analysis of the inhibitor incidence regardless of subsequent positive or negative inhibitor test results. Measurements of FVIII inhibitors were performed using a heat-treated Nijmegen FVIII Bethesda assay validated according to international recognised

guidelines. Blood sampling for the inhibitor test was performed at least 72 hours after last administration of N8-GP to allow for wash-out of FVIII that otherwise could interfere with the test. Less than 72 hours was acceptable in a patient with increased clearance (e.g., in an already confirmed inhibitor patient).

Adverse Events

The investigator was responsible for detecting, documenting, recording and following up on events that met the definition of an AE or a SAE as detailed in the protocol. All AEs either observed by the investigator or reported spontaneously by the patients were to be recorded by the investigator and evaluated. This included events from the first trial-related activity after the patient's parent(s)/LAR(s) has signed the informed consent until the end of trial visit. In addition, the patients were to be asked at each visit whether they had had any AEs (including any changes in concomitant illness or new illnesses) since the last visit. The investigator was to assess all AEs with regards to seriousness (serious, non-serious), severity (mild, moderate, severe), causality (probable, possible, unlikely), and final outcome (recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/resolved, fatal, unknown) by following the definitions in the trial protocol. The investigator was required to report SAEs to Novo Nordisk by forwarding the completed AE form within 24 hours and the Safety Information Form within 5 days. In addition to the standard reporting of AEs/SAEs, certain event types were designated medical events of special interest (MESI) and required additional data collection via dedicated event forms.

7.2. Results

Incidence of Inhibitors (including Primary Endpoint)

Table 11: Incidence of inhibitory antibodies against FVIII (≥0.6BU) – primary endpoint – main + extension

	Pre-prophylaxis	Prophylaxis	Total
Number of patients	55	68	80
Number of patients with inhibitory antibodies*	11	10	21
Number of patients at risk**	21	57	70
Rate of inhibitory antibodies***			
Estimated inhibitor rate	0.524	0.175	0.300
1-sided 97.5 % upper confidence limit	0.743	0.299	0.421

Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns, with data from the relevant period.
The inhibitor antibodies were measured using a heat modified Nijmegen FVIII Bethesda assay.
* All patients with neutralising antibodies (>=0.6 BU) are included in the numerator.
** Any patient with a minimum of 10 EDs plus any patient with acquired inhibitory antibodies is included in the denominator.
*** Estimates are based on exact calculations for a binomial distribution.
The sample excludes a patient that tested as positive inhibitor prior to starting the trial.

Figure 5: Kaplan-Meier plot – time-to positive inhibitors – main + extension

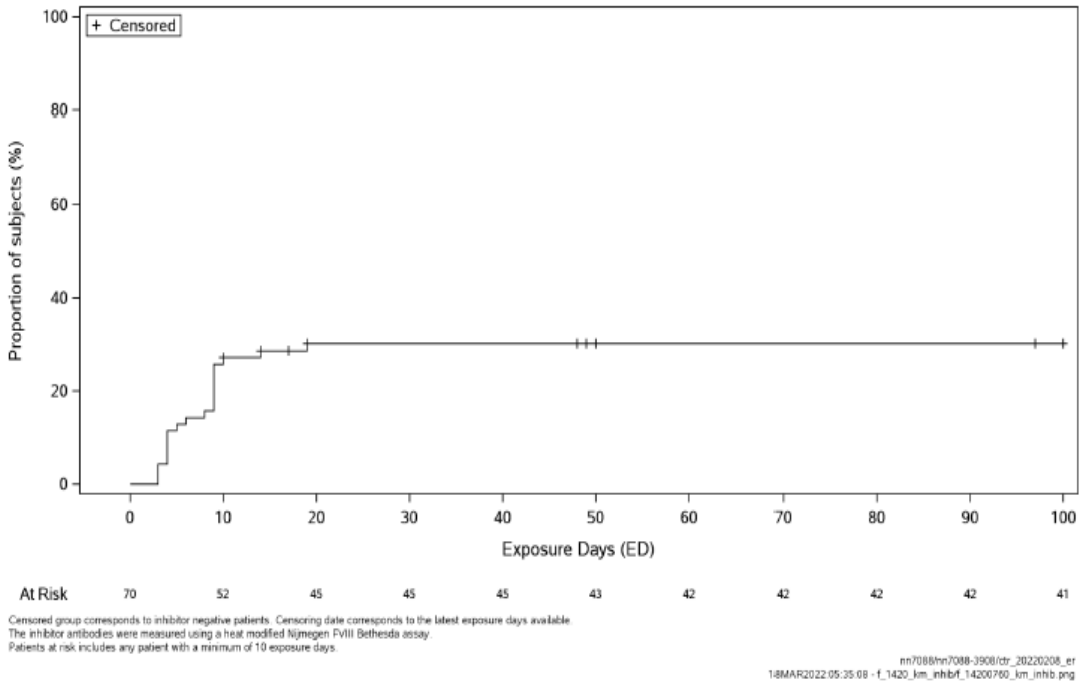
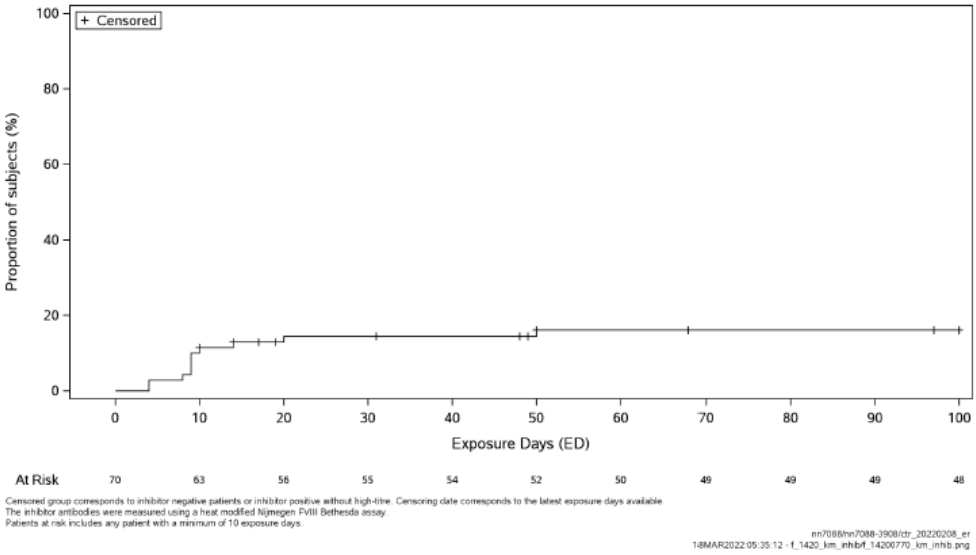


Table 12: Incidence of high titre inhibitory antibodies against FVIII (>5BU) – main + extension

	Pre-prophylaxis	Prophylaxis	Total
Number of patients	55	68	80
Number of patients with inhibitory antibodies*	3	8	11
Number of patients at risk**	17	64	70
Rate of inhibitory antibodies***			
Estimated inhibitor rate	0.176	0.125	0.157
1-sided 97.5 % upper confidence limit	0.434	0.232	0.264

Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns, with data from the relevant period.
The inhibitor antibodies were measured using a heat modified Nijmegen FVIII Bethesda assay.
* All patients with high titre antibodies (>5 BU) are included in the numerator.
** Any patient with a minimum of 10 EDs plus any patient with acquired inhibitory antibodies is included in the denominator.
*** Estimates are based on exact calculations for a binomial distribution.
The sample excludes a patient that tested as positive inhibitor prior to starting the trial.

Figure 6: Kaplan-Meier plot – time-to positive high-titre inhibitors – main + extension



Development of anti-N8-GP, anti-PEG IgM and anti-PEG IgG binding antibodies

Plasma samples were collected at baseline and during the trial for assessment of:

- Anti-N8-GP binding antibodies (no cross-reactivity to anti-PEG antibodies)
- Anti-PEG IgM binding antibodies
- Anti-PEG IgG binding antibodies

Due to the small sample volumes collected in young children, some patient samples could not be measured for all 3 types of antibodies. Of a total of 81 exposed patients, 42 patients (51.9%) developed anti-N8-GP binding antibodies, 22 patients (27.1%) developed anti-PEG IgM binding antibodies and 51 patients (63.0%) developed anti-PEG IgG binding antibodies.

Table 13: Overview of anti-drug antibody findings

	Pre-Prophylaxis N (%)	Prophylaxis N (%)	Total N (%)
Number of patients	55	69	81
Number of patients with confirmed inhibitor	15	19	21
Confirmed anti-N8-GP antibodies			
Missing - Positive	8 (14.5)	5 (7.2)	8 (9.9)
Missing - Negative	6 (10.9)	5 (7.2)	6 (7.4)
Negative - Positive	21 (38.2)	32 (46.4)	34 (42.0)
Negative - Negative	19 (34.5)	25 (36.2)	30 (37.0)
Negative - Missing	1 (1.8)	0	1 (1.2)
Positive - Positive	0	2 (2.9)	2 (2.5)
Confirmed anti-PEG IgG antibodies			
Missing - Positive	8 (14.5)	6 (8.7)	9 (11.1)
Missing - Negative	5 (9.1)	6 (8.7)	6 (7.4)
Missing - Missing	1 (1.8)	0	1 (1.2)
Negative - Positive	26 (47.3)	39 (56.5)	42 (51.9)
Negative - Negative	8 (14.5)	7 (10.1)	8 (9.9)
Negative - Missing	1 (1.8)	0	1 (1.2)
Positive - Positive	6 (10.9)	11 (15.9)	14 (17.3)
Confirmed anti-PEG IgM antibodies			
Missing - Positive	4 (7.3)	2 (2.9)	4 (4.9)
Missing - Negative	9 (16.4)	9 (13.0)	10 (12.3)
Negative - Positive	9 (16.4)	17 (24.6)	18 (22.2)
Negative - Negative	25 (45.5)	27 (39.1)	31 (38.3)
Negative - Missing	1 (1.8)	0	1 (1.2)
Positive - Positive	5 (9.1)	11 (15.9)	13 (16.0)
Positive - Negative	2 (3.6)	3 (4.3)	4 (4.9)

N: Number of patients.
Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns, with data from the relevant period.
Patients with at least one positive/reactive sample post-N8-GP treatment are accounted as having a positive/reactive post-N8-GP treatment status.
First status is measured at the trial baseline. The second status is measured after first exposure to N8-GP.

Table 14: Overview on inhibitor and antibody test during trial

	FVIII Inhibitors	Anti-N8GP	Anti-PEG IgM	Anti-PEG IgG	Anti-CHO HCP
Number of patients	80	80	80	79	67
Anytime during trial, N (%)					
N	1109 (100.0)	1091 (100.0)	371 (100.0)	627 (100.0)	135 (100.0)
Positive	122 (11.0)	258 (23.6)	63 (17.0)	310 (49.4)	10 (7.4)
Negative	987 (89.0)	833 (76.4)	308 (83.0)	317 (50.6)	125 (92.6)

Table 15: Overview on anti-drug antibody findings

	Inhibitor patients N (%)	Non-Inhibitor patients N (%)	Total N (%)
Number of patients	21	59	80
Incidence of antibodies post-baseline			
Anti-N8-GP	20 (95.2)	22 (37.3)	42 (52.5)
Anti-PEG IgG	12 (57.1)	38 (64.4)	50 (62.5)
Anti-PEG IgM	7 (33.3)	15 (25.4)	22 (27.5)
Anti-CHO HCP	1 (4.8)	6 (10.2)	7 (8.8)
Patients with anti-N8-GP and anti-IgG/IgM antibodies	15 (71.4)	18 (30.5)	33 (41.3)

N: Number of patients
Patients with at least one post baseline positive antibody test are included.
nn7088/nn7088-3908/qa_ema_20220607
14SEP2022:12:09:32 - qa_incid_antibod.sas/qa_antibod_devp.txt

Cross-reference: Appendix 1, Table 1

Adverse Events

The presented results are based on treatment emergent adverse events (TEAEs). There were no non-treatment emergent AEs (i.e., AEs occurring in a patient before being exposed to N8-GP). All TEAEs are referred to as AEs. AEs are presented and described for the joined main and extension phases (main + extension). A direct comparison of the pre-prophylaxis and prophylaxis patient subgroups is not applicable as patients who switched treatment regimen during the trial are represented in both subgroups.

Table 16: Overview of adverse events – main + extension

	Pre-prophylaxis N (%) E [R,F]	Prophylaxis N (%) E [R]	Total N (%) E [R]
Number of patients	55	69	81
Total time in trial (years)	27.07	197.23	224.30
Total number of exposure days	428	16242	16670
All adverse events	40 (72.7) 116 [4.29,0.27]	64 (92.8) 644 [3.27]	78 (96.3) 760 [3.39]
Serious adverse events	18 (32.7) 24 [0.89,0.06]	34 (49.3) 56 [0.28]	48 (59.3) 80 [0.36]
Adverse events by severity			
Severe	11 (20.0) 11 [0.41,0.03]	15 (21.7) 20 [0.10]	23 (28.4) 31 [0.14]
Moderate	17 (30.9) 28 [1.03,0.07]	25 (36.2) 70 [0.35]	36 (44.4) 98 [0.44]
Mild	35 (63.6) 77 [2.84,0.18]	58 (84.1) 554 [2.81]	72 (88.9) 631 [2.81]
Missing	-	-	-
Adverse events by outcome			
Recovered/resolved	39 (70.9) 103 [3.81,0.24]	60 (87.0) 623 [3.16]	74 (91.4) 726 [3.24]
Recovering/resolving	1 (1.8) 1 [0.04,0.00]	3 (4.3) 3 [0.02]	4 (4.9) 4 [0.02]
Recovered/resolved with sequelae	3 (5.5) 3 [0.11,0.01]	2 (2.9) 2 [0.01]	5 (6.2) 5 [0.02]
Not recovered/not resolved	5 (9.1) 8 [0.30,0.02]	14 (20.3) 15 [0.08]	18 (22.2) 23 [0.10]
Fatal	-	-	-
Unknown	1 (1.8) 1 [0.04,0.00]	1 (1.4) 1 [0.01]	2 (2.5) 2 [0.01]
Missing	-	-	-
Adverse events by relationship			
Probably or possibly related	19 (34.5) 25 [0.92,0.06]	26 (37.7) 31 [0.16]	43 (53.1) 56 [0.25]
Unlikely related	34 (61.8) 91 [3.36,0.21]	57 (82.6) 613 [3.11]	68 (84.0) 704 [3.14]
Adverse events leading to withdrawal*	4 (7.3) 4 [0.15,0.01]	3 (4.3) 3 [0.02]	6 (7.4) 7 [0.03]

All adverse events in this table are treatment emergent.
Patients who switched from pre-prophylaxis to prophylaxis are represented in all columns, with data from the relevant period.
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 year in trial (E/total time in trial).
[F]: number of adverse events per EDs (E/total number of EDs).
*Two patients who withdrew due to adverse events are not summarised here, since "action taken" for those AEs was wrongly reported in the AE form instead of "Drug withdrawn".

Deaths and other serious adverse events

No deaths were reported.

Serious adverse events (SAEs): A total of 80 SAEs in 48 patients (59.3%) were reported during the trial (main+extension phase), corresponding to an overall rate of 0.36 SAEs per patient year in trial.

The most frequent SAEs (24 events) were reported in SOC 'blood and lymphatic system disorders', of which 23 events in 22 patients were reported under PT 'factor VIII inhibition' (event rate 0.10 AEs per patient year in trial). Second most frequent SAEs (19 events) were in 12 patients reported under SOC 'infections and infestations' (event rate 0.08 AEs per patient year in trial), distributed on 17 different PTs.

Twenty-seven (27) SAEs were evaluated by investigator as probably or possibly related to N8-GP, of which 22 SAEs alone were reported with preferred term 'factor VIII inhibition'. Seventeen (17) of these 27 events were recovered/resolved, and 1 event was recovered/resolved with sequelae. Out of remaining 9 events, outcome was unknown for 2 events and not recovered/not resolved for remaining 7 events.

Table 17: SAEs reported as life-threatening – main + extension

Patient ID/ Age(mo)/ Treatment	AE no	System organ class/ Preferred term/ Investigator's description	Days since first/ latest dose	Age(mo)/ ED at onset	Onset/ Resolution date	Duration (days)	Serious/ Life**/ MESI (Y/N)	Severity/ Relationship	Action/ Outcome
[redacted] 50-75 U/Kg	5	Nervous system disorders / Cerebral haemorrhage/ LARGE FRONTAL INTRACEREBRAL HEMORRHAGE	334/ 50	[redacted] 3	[redacted]	47	Y/ Y/ N	Severe/ Unlikely	Dose Not Changed/ Recovered/resolved with sequelae
[redacted] 50-75 U/Kg	3	Nervous system disorders / Cerebral haemorrhage/ INTRACEREBRAL HEMORRHAGE	56/ 3	[redacted] 11	[redacted]	29	Y/ Y/ N	Severe/ Unlikely	Drug Interrupted/ Recovered/resolved
[redacted] 50-75 U/Kg	2	Nervous system disorders / Spinal epidural haematoma/ EPIDURAL HAEMATOMA AT THE CERVICAL THORACIC SPINE FROM C6/C7 TO T4	6/ 6	[redacted] 1	[redacted]	24	Y/ Y/ N	Severe/ Unlikely	Drug Withdrawn/ Recovered/resolved
[redacted] 50-75 U/Kg	5	Injury, poisoning and procedural complications / Wound haemorrhage/ HOSPITALIZATION REBLEEDING OF LACERATION WOUND FROM DORSUM OF TONGUE	20/ 1	[redacted] 7	[redacted]	7	Y/ Y/ N	Severe/ Unlikely	Dose Not Changed/ Recovered/resolved
[redacted] 50-75 U/Kg	2	Blood and lymphatic system disorders/ Factor VIII inhibition/ FVIII INHIBITOR	211/ 1	[redacted] 6	[redacted] -	-	Y/ Y/ Y	Severe/ Possible	Drug Withdrawn/ Not recovered/not resolved

ED: exposure day.
MESI: medical event of special interest.
Y: yes, N: no.
mo: month.
**Life: indicates whether a serious AE was life-threatening or not (only for serious AEs).
MedDRA version 22.0

Adverse events leading to withdrawal from the trial

There were 7 AEs in 6 patients that led to withdrawal during the trial. All 7 AEs were severe and possibly or probably related to N8-GP. Five (5) events were also SAEs. Two (2) events were related to inhibitor development, 2 events were related to antibodies against N8-GP, 1 event was related to lack of efficacy from treatment, 1 event was related to increased heart rate, and 1 event was related to drug hypersensitivity.

Medical events of special interest

Medical events of special interest (MESIs) were presented by standardised MedDRA queries (SMQ) categories FVIII inhibitors, hypersensitivity, medication errors, anaphylactic reactions, and thromboembolic events (see Section 9.7.2 for details on SMQ categories). There were no MESIs within SMQ categories medication errors and anaphylactic reactions. There were a total of 64 MESIs in 43 patients during main + extension phase, and all were within SMQ categories FVIII inhibitors, hypersensitivity, and thromboembolic events.

A total of 35 MESIs in 32 patients were within SMQ category FVIII inhibitors; 29 MESIs in 26 patients were within SOC 'blood and lymphatic system disorders' with PT 'factor VIII inhibition', while 6 MESIs in 6 patients were within SOC 'investigations' with PT 'anti factor VIII antibody positive'.

A total of 26 MESIs in 19 patients were within SMQ category hypersensitivity; 16 MESIs in 13 patients were within SOC 'skin and subcutaneous tissue disorders' distributed on 9 different PTs (angioedema, dermatitis atopic, dermatitis contact, eczema, rash, rash erythematous, rash generalised, rash maculo-

papular, and urticaria. Another 10 MESIs were distributed on 5 SOCs and 6 PTs (blepharitis allergic, conjunctivitis allergic, lip swelling, catheter site rash, drug hypersensitivity, and rhinitis allergic.

A total of 3 MESIs in 2 patients were within SMQ category thromboembolic events; 1 MESI was within SOC 'injury, poisoning and procedural complications' and PT 'shunt occlusion'; 1 MESI was within SOC 'product issues' and PT 'device occlusion'; 1 MESI was within SOC 'surgical and medical procedures' and PT 'central venous catheterisation'. Twenty-eight (28) of the 64 MESIs were also SAEs, including 23 events alone with PT 'FVIII inhibition'.

Clinical laboratory evaluation

No clinically significant changes were observed for haematology parameters during the trial.

No clinically significant changes were observed for biochemistry parameters during the trial.

Vital signs, physical findings and other observations related to safety

No clinically significant changes over time in vital signs or body measurements were apparent.

Abnormal physical examination findings generally include findings related to haemophilia A or to childhood in general.

No abnormal changes over time were apparent for body measurements.

Technical complaints

There were 4 technical complaints. Two technical complaints were related to missing content or functionality of the trial injection kit. No samples were returned for investigation. One technical complaint was related to the observation of white flaky slivers in a vial (N8- GP 500 IU/vial, batch number FR40065). The product was found normal during subsequent investigations. One technical complaint was related to the observation of an already broken vial (N8- GP 2000 IU/vial, batch number HR40835) when opening the box with trial product. A handling fault was verified.

7.3. Discussion

Immunogenicity

Whereas the expected incidence of inhibitor formation in PTPs for FVIII products is usually stated as "uncommon" (i.e. frequencies range from 1/1000 to 1/10000), the formation of antibodies in PUPs is a major concern for the treatment and thus every PUP requires close monitoring with regards to treatment performance and inhibitor development during treatment initiation with FVIII products (see also respective GL on the clinical investigation of recombinant and human plasma-derived factor VIII products EMA/CHMP/BPWP/144533/2009 rev. 2). According to GL "*formal PUP studies are not required*", but it is agreed with the MAH that the occurrence of inhibitors against FVIII highly depends on the specific product at hand and PUPs are at the highest risk to develop a neutralising antibody against exogenous FVIII. Therefore, the availability of data regarding antibodies in PUPs is acknowledged. The chosen primary endpoint (incidence of FVIII inhibitors) is in line with this argumentation.

According to the EPAR for Esperoct, at the time of authorisation two paediatric patients (<12 years) had an unconfirmed positive tests for FVIII inhibitors in trial 3885. However, previously treated patients (as investigated in study 3885) do not offer a good comparison with regards to immunogenic events targeted against the medication. Calvez et al. (2014) evaluated recombinant FVIII products regarding their potential to trigger inhibitor development in PUPs and concluded that 37.6% PUPs develop inhibitors and 20.8% develop high-titre inhibitors across several tested rFVIII products. During study 3908 26.25% of PUPs developed inhibitory antibodies against FVIII (21 of 80 patients) and 13.75% of subjects developed high titre inhibitory ABs against FVIII (11 of 80 patients). Thus, incidence of FVIII inhibitor formation for Esperoct in PUPs is very common (i.e. frequency ≥1/10 patients), but appears comparable to other recombinant FVIII products. According to the provided Kaplan-Meier plots and table 14.3.5.10 (please refer to the study report), the majority of FVIII inhibitors developed before ED50, which is in line with the expected highest risk during the first 50 EDs as depicted in the GL. It is reported that 52.5% of PUPs had anti- N8-GP antibodies, 81% of PUPs had anti-PEG IgG (63.3% developed anti-PEG IgG after exposure to Esperoct and 17.7% had anti-PEG IgG at baseline), 27.5% of PUPs had anti-PEG IgM and 8.8% of PUPs had anti-CHO HCP antibodies (incidences based on patients with at least one post baseline positive antibody test). In total 41.3% of PUPs had anti-drug antibodies against more than one drug moiety (i.e. anti N8-GP and anti-PEG). Anti-PEG antibodies (IgG and IgM) were associated with the observed transient decrease in IR for a subset of PUPs (see discussion on efficacy for more details). Upon request, the MAH clarified that no PTPs were observed with consecutive low IR during trials 3859 and 3885. Also no decrease in IR was observed in paediatric PTPs with pre-existing anti-PEG antibodies at baseline. Thus, the possible correlation of anti-PEG antibodies and transient low IR appears conclusive only for PUPs. Information regarding FVIII inhibitors is reflected in the SmPC section 5.1 (as per SmPC guideline rev.2). As patients <12 years are currently not licensed for the treatment with Esperoct, it appears sufficient to include a respective statement regarding transient low IR in section 5.1 (as per SmPC guideline rev. 2). However, it is noted that potentially reduced IR is an important identified risk that is considered clinically very relevant and should be reflected as a warning statement in the SmPC (section 4.4) once a label update is submitted to extend the indication to PUPs <6 years. Furthermore, closer monitoring of FVIII levels upon treatment initiation with this pegylated FVIII product in PUPs should be evaluated in more detail once licensure for paediatric subjects is requested. Information on PUPs is included in sections 4.8 and 5.1 of the SmPC.

Adverse Events

The reported AEs for PUPs are mostly single PT events except for FVIII inhibition (23 events in 22 patients), pneumonia (3 events in 1 patient), head injury (3 events in 3 patients), cerebral haemorrhage (2 events in 2 patients), anti-factor VIII antibody positive (2 events in 2 patients) and respiratory failure (2 events in 1 patient). The rate of "all AEs" for PUPs in trial 3908 is comparable to the rate as reported for previously treated patients of the same age group (<6 years) in the current EPAR (96.3% and 94.1% of patients, respectively; Note that study 3908 comprises more subjects and a higher number of exposure days). However, the rate of serious AEs appears much higher for PUPs (59.3% and 29.4% of patients, respectively) and more PUPs had severs AEs (28.4% and 20.6% of patients, respectively). Also, the rate of AEs leading to withdrawal is mildly higher for PUPs (7.4% and 5.9%) of patients, respectively. No death is reported for PUPs in study 3908. All MESIs (64 MESIs in 43 patients) were within the SMQ categories FVIII inhibitors, hypersensitivity, and thromboembolic events, which is in line with identified risks for PTPs. Most of the 80 SAEs in study 3908 were related to PT FVIII inhibition (n=23 events in n=22 patients) and one of those events was reported as life threatening. Upon request, the MAH clarified that the higher rate of SAEs in PUPs compared to PTPs can be attributed to the high rate of inhibitor-related SAEs in PUPs compared to the PTPs and the lower median age of the PUPs from trial 3908 (8 months) compared to the PTPs from trial 3885 (3 years) of the same age group (<6 years). Information

regarding FVIII inhibitors in PUPs is reflected in the SmPC section 4.8 even though paediatric patients are currently not licensed (as depicted in the core SmPC for human plasma derived and recombinant coagulation factor VIII products EMA/CHMP/BPWP/1619/1999 rev. 3 and SmPC guideline rev.2; see SmPC; see also assessment of responses in section 11 and 12.).

Importantly, 5 SAEs were reported for the SOC Nervous system disorder including PTs cerebral haemorrhage (2 events in 2 patients) as well as febrile convulsion, seizure and spinal epidural haematoma (1 event in 1 patient for each PT). Three of those SAEs in the SOC Nervous system disorders were also considered life threatening (2 cerebral haemorrhage and 1 spinal epidural haematoma; in total 5 serious adverse events were reported as life threatening). In this aspect it should be noted that currently a PASS is ongoing to evaluate potential negative effects of Esperoct on brain development in subjects <12 years. In line with this, the benefit-risk for this age group was concluded negative during initial MAA. The underlying effect is expected to be an accumulation of PEG in the choroid plexus. Thus, uncertainty remains if any risks related to long-term exposure to PEGylated FVIII exist. Further details on this aspect are expected with results from the ongoing PASS. However, the study at hand cannot provide further detail on this aspect, but results from study 3908 further underline the need to await results from the ongoing PASS that is addressing potential effects of Esperoct on nervous system development. In conclusion, the benefit-risk of Esperoct for subjects <12 years remains negative based on safety concerns, also with the available data regarding PUP <6 years.

7.4. Direct Healthcare Professional Communication

The (Co-)Rapporteur's comments on the DHPC and the draft communication plan are provided below.

Rapporteurs comment on DHPC:

A Direct Healthcare Professional Communication (DHPC) is not considered necessary, as no immediate changes regarding the safety profile or therapeutic strategy become evident for the evaluated product. Requested changes within this type II variation address the principal observation of previously untreated subjects <6 years in the scope of a clinical trial, which, however, does not reassure the treatment of subjects <12 year. The benefit-risk for Esperoct remains negative for subjects <12 years. A PASS is ongoing to address safety concerns in this age group.

8. Changes to the Product Information

As a result of this variation, section(s) 4.2 and 5.1 of the SmPC are being updated to reflect the available data on PUPs. The Package Leaflet (PL) is requested to be updated accordingly.

Comments on updated sections and additional requests are provided directly in the PI document.