28 March 2019
EMA/462252/2019
Human Medicines Evaluation Division

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

NovoEight

turoctocog alfa

Procedure no: EMEA/H/C/002719/P46/008

Note

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

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Table of contents

1. Introduction

On 4th January 2019, the MAH submitted a completed paediatric study, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

NovoEight (Turoctocog alfa) is a third generation recombinant coagulation factor VIII (rFVIII) product. In the European Union (EU), NovoEight was approved by the European medicines agency (EMA) on 13 November 2013 for treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Turoctocog alfa can be used for all age groups.

The clinical trial NN7008-3809 is part of the Paediatric Investigation Plan (PIP), decision number EMEA-000428-PIP-01-08-MO3. The PIP consists of 4 paediatric trials, where NN7008-3908 is the last trial to be completed. An overview of the paediatric trials for NovoEight PIP is provided in the annexed line listings.

2.2. Information on the pharmaceutical formulation used in the study

Turoctocog alfa is a B-domain truncated recombinant human coagulation factor VIII without any other modifications in the amino acid sequence. It is produced by recombinant DNA technology in Chinese hamster ovary cells, and prepared without the addition of any human or animal derived protein in the cell culture process, purification or final formulation. It was supplied as a sterile, freeze-dried powder in single-use vials of 250 IU/vial and 2000 IU/vial each to be reconstituted with 4.3 mL 0.9% sodium chloride for injection. After reconstitution, each 250 IU vial contained 62.5 IU/mL of turoctocog alfa and each 2000 IU vial contained 500 IU/mL of turoctocog alfa. The reconstituted solution was colourless, almost clear with a pH of 6.9 and was not to be further diluted.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for study NN7008-3809, a Phase 3a trial evaluating the safety and efficacy of the B-domain truncated rFVIII in the prevention and treatment of bleeding episodes in paediatric previously untreated patients (PUPs) with severe Haemophilia A without inhibitors. The study was given the title “guardian 4”.
Initiation date of this study was 17 September 2012 and primary completion date 16 August 2017. Global completion date defined as actual last patient last visit (LPLV) was 27 June 2018, however, 3 patients are on ITI and continue treatment under Protocol exception criteria (criteria: patients with inhibitor will be allowed to receive inhibitor treatment for up to 24 months). Data about these 3 patients are to be submitted separately as an addendum to the final report after trial completion which was expected for December 2018. It was noted that this procedure has been agreed with the EMA.

Clinical study NN7008-3809 (Guardian 4)

Safety and efficacy of turoctocog alfa in prevention and treatment of bleeds in paediatric previously untreated patients with Haemophilia A

Description

Methods

Objective(s)

Primary objective:

To evaluate safety of turoctocog alfa in paediatric previously untreated patients with haemophilia A

Secondary objectives:

- To evaluate efficacy and safety of turoctocog alfa in treatment of bleeds in paediatric PUP with haemophilia A

- To evaluate preventive effect of turoctocog alfa on bleeds in paediatric PUP with haemophilia A

- To evaluate patient reported outcomes (PRO) impact of turoctocog alfa treatment

- To evaluate the health economic (HE) impact of turoctocog alfa treatment

Study design

Guardian 4 was a multi-centre, multi-national, non-randomised, open-label, safety and efficacy trial in a male paediatric population of PUPs (<6 years of age) with severe haemophilia A (FVIII level ≤1%). There was only one treatment arm and no comparator.

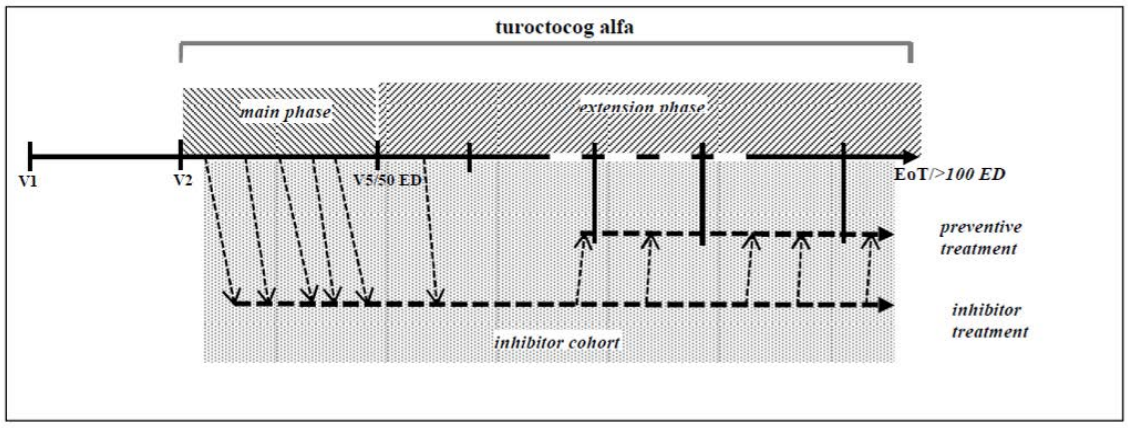
The trial consisted of two phases: the main phase including the screening and 4 subsequent visits, and an extension phase with a rolling visit schedule consisting of 6 planned visits (including 4 dispensing visits)

per year. Each patient was to receive turoctocog alfa doses of 15−60 IU/kg body weight (BW) administered as an i.v. injection for the prevention of bleeding (treatment regimens are outlined below). Patients who enrolled into the trial could postpone initiation of preventive treatment until a maximum of two treatment requiring bleeding episodes have occurred, or until the patient's second birthday. The investigator decided what dose of turoctocog alfa to give based on the child's clinical profile. It was recommended to have at least one day between each turoctocog alfa preventive dose. Patients waiting to start a preventive regimen were treated on demand for bleeds as they occurred. Patients were allowed to undergo minor or major surgical procedures during the trial. Upon completion of the surgery the patient could resume preventive treatment as before the surgery.

In the event that a patient developed inhibitors during the trial he could continue treatment with turoctocog alfa and follow an alternative visit schedule. These patients were considered as a separate 'inhibitor' cohort and evaluated accordingly. They were offered continued treatment with turoctocog alfa for up to 24 months. Treatment during the inhibitor cohort included Immune Tolerance Induction (ITI) as well as smaller dose adjustments in cases of clinically insignificant inhibitors. Upon entering the cohort, inhibitor patients could hold off from starting ITI treatment and be in a pre-ITI period, where they could either receive prophylaxis treatment with turoctocog alfa or no prophylactic treatment at all; similarly, at completion of ITI treatment the investigator could choose to keep the patient in a post-ITI period before allowing the patient to complete the cohort and enter the following study phase.

Inhibitor treatment refers to the ITI part of the inhibitor cohort. In the event that the inhibitor disappeared (<0.6 Bethesda units [BU]) during inhibitor cohort, the patient could continue in the extension phase at a time point decided by the investigator, and resume/start preventive treatment as recommended in the protocol. However, patients with inhibitors that persisted beyond 24 months of 'inhibitor treatment' or patients with a decrease less than < 20% from peak level inhibitor within the first 12 months of 'inhibitor treatment' were to be withdrawn from the trial. In addition, the patients who were not started on ITI treatment within 6 months from the date of confirmation of positive FVIII inhibitor were also to be withdrawn from the trial.

Figure 1 : Trial design



An interim analysis (safety interim analysis) was performed to assess the incidence of inhibitors when the first 25 patients had performed visit 4 (20−25 ED), or had developed an inhibitor before visit 4. The data cut-off date for this analysis was 24 June 2015. Another interim analysis was performed upon completion of the main phase of the trial i.e. when an aggregated number of ≥50 patients had either received treatment with turoctocog alfa for at least 50 EDs or developed FVIII inhibitors. The cut-off date of this analysis was 13 February 2017. Data described in this clinical trial report are from the main phase, the extension phase and the combined (cumulative) main and extension phases of the trial. The main phase completed once an aggregated number of ≥50 patients had either received treatment with turoctocog

alfa for at least 50 ED or developed inhibitors. The extension phase concluded once ≥50 patients achieved at least 100 ED.

Study population /Sample size

A total of 60 patients were enrolled in the trial and received at least one dose of turoctocog alfa.

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 diagnosed with congenital severe haemophilia A (FVIII level ≤1%)
3. Age <6 years
4. No prior use of purified clotting FVIII products (previous exposure, equal to or less than 5 ED to blood components, e.g. cryoprecipitate, fresh frozen plasma, was accepted) including commercially available NovoEight/Novoeight

The exclusion criteria were as follows:
1. Known or suspected allergy to hamster protein or intolerance to trial product(s) or related products
2. Previous participation in this trial defined as withdrawal after administration of trial product
3. Congenital or acquired coagulation disorders other than haemophilia A
4. Any history of FVIII inhibitor
5. On-going or planned treatment during the trial with immunomodulatory agents (e.g. intravenous immunoglobulin (IVIG)), routine systemic corticosteroids)
6. Any disease or condition which, judged by the investigator, could imply a potential hazard to the patient, interfere with the trial participation or trial outcome including renal and/or liver failure
7. Unwillingness, language or other barriers precluding adequate understanding and/or cooperation from parents and/or legal representatives and child
8. The receipt of any investigational product within 30 days prior to inclusion in this trial

Treatments

Treatment with turoctocog alfa was evaluated during the following 3 trial periods:

Main:

- On-demand: Visit 2 to first preventive dose. This group included children ≤2 years receiving on-demand treatment while waiting to start on a preventive regimen.

- Preventive: Patients on prophylactic factor VIII replacement therapy until Visit 5 or until development of inhibitor, whichever came first.

Extension (preventive): Prophylactic treatment administered from completion of the main phase or completion of the inhibitor cohort until the end-of-trial visit.

Inhibitor cohort: Patients who developed an inhibitor during the course of the trial and followed an alternative treatment regimen.

Table 9-1 Overview of treatment regimens

Trial product	Treatment	Type	Total daily Doses, IU/kg	Frequency	Targeted level of FVIII
rFVIII (turoctocog alfa)	Preventive	Individual	15−50	Once weekly	Local practice & guidelines
rFVIII (turoctocog alfa)	Preventive	Individual	20−60	Two times weekly	Local practice & guidelines
rFVIII (turoctocog alfa)	Preventive	Individual	20−60	Three times weekly	Local practice & guidelines
rFVIII (turoctocog alfa)	Preventive	Individual	20−50	Once every second day	Local practice & guidelines
rFVIII (turoctocog alfa)	Treatment of bleeds	Individual	Investigator's discretion[b]	Investigator's discretion	>0.50 IU/mL
rFVIII (turoctocog alfa)	Surgery	Individual	Investigator's discretion[b]	Investigator's discretion	>0.50 IU/mL[a] Local practice & guidelines
rFVIII (turoctocog alfa)	Inhibitor	Individual	Investigator's discretion[b]	Investigator's discretion	NA

[a]Pre-surgery and during surgery treatment
[b]The maximum daily dose of turoctocog alfa for treatment of a bleed, and/or during immune tolerance induction treatment for patients with inhibitors, could not exceed 200 IU/kg with a maximum dose per infusion of 100 IU/kg.

Table 9-2 Guide for dosing in bleeding episodes[a]

Degree of haemorrhage	FVIII level required (%) (IU/dL)	Frequency of doses (hours)/Duration of therapy (days)
Early haemarthrosis, muscle bleeding or oral bleeding	20−40	Repeat every 12 to 24 hours until the bleeding episode as indicated by pain is resolved or healing achieved
More extensive haemarthrosis, muscle bleeding or haematoma	30−60	Repeat injection every 12 to 24 hours for 3-4 days or more until pain and acute disability are resolved
Life-threatening haemorrhages	60−100	Repeat injection every 8 to 24 hours until threat is resolved

[a]Novo Nordisk company core data sheet for turoctocog alfa

Duration of treatment: All patients were offered participation in the trial until either turoctocog alfa was commercially available in the relevant country or until the trial, part of the trial or a trial site was terminated by Novo Nordisk, or by a relevant authority for any reason in the relevant country. In any event, the LPLV for the trial should be no later than 30 June 2018 regardless of turoctocog alfa commercialisation in the relevant country, with the following exceptions:

1. Patients will be allowed to achieve at least 100 ED with trial product

2. Patients with inhibitor will be allowed to receive inhibitor treatment for up to 24 months

Outcomes/endpoints

- Primary safety endpoint
    1. Incidence rate of FVIII inhibitors (≥0.6 BU) evaluated for the main phase of the trial

- Secondary safety endpoints (evaluated for the main phase of trial, extension phase, and combined main and extension phases of the trial).
    1. Frequency of adverse events (AEs) and serious adverse events (SAEs) reported during the trial period
    2. Incidence rate of clinically relevant inhibitors defined as an inhibitor titre (≥0.6 BU) combined with a decreased recovery (<66% of expected level)
    3. Incidence rate of high-titre inhibitors defined as inhibitor titre ≥5 BU
    4. Incidence rate of FVIII inhibitors (≥0.6 BU)

- Secondary efficacy endpoints
    1. Haemostatic effect of turoctocog alfa on treatment of bleeds assessed on a predefined four-point scale: Excellent, Good, Moderate and None
    2. Annualised bleeding rate
    3. Number of turoctocog alfa infusions required per bleed
    4. Total consumption of turoctocog alfa per patient (prevention, treatment of bleeds and during surgery) per month and annualised value
    5. Consumption of turoctocog alfa (IU/kg/bleed) per bleed
    6. Consumption of turoctocog alfa (IU/kg/ months) for bleed prevention

- Patient reported outcomes (PRO) and Health economics (HE) endpoints:
    1. Change in total scores for parent reported treatment satisfaction
    2. Health resource utilization and caregiver burden associated with bleeds

Statistical Methods

Sample size:
No formal sample size calculations were performed, but 50 patients were expected to give adequate precision for the estimate of inhibitor formation in PUP. Therefore, the trial enrolled 60 patients to allow for a 15% drop-out rate and achieve a target sample size of 50 patients completing the trial.

Definition of analysis sets:
Both the full analysis set (FAS) and safety analysis set included all dosed patients with data after dosing. All main descriptions and analyses of efficacy were based on the FAS. The analyses of safety were based on the safety analysis set.

Efficacy:

- The haemostatic effect of turoctocog alfa was summarised by frequency tables containing count and percentages of all bleeds and assessed on a predefined four point scale: excellent, good, moderate and none. The effect was also summarised by cause, site, time and classification of bleed.
- Annualised number of bleeds in total and by cause of bleeding (spontaneous or traumatic) were estimated by a Poisson model allowing for over-dispersion and presented with a 95% confidence interval (CI). In the analysis of this endpoint, patients were to be included only if they received at least 2 doses of trial product before testing positive for inhibitors. An additional analysis of annualised bleeding rate (ABR) was performed to calculate the bleeding rate for all dosing frequencies.
- The number of infusions of turoctocog alfa required per bleed was calculated as the number of infusions of turoctocog alfa used in the time period from start of the bleed to stop of the bleed.
- Consumption (IU/kg BW) was listed in total by patient. For bleeds, the consumption was calculated based on the number of doses from start to stop of bleed. Consumption for preventive treatment was calculated as the consumption of preventive doses over a period of time.

Safety:

- Primary endpoint: The incidence rate of inhibitors defined as inhibitor titres ≥0.6 BU for the main phase of the trial was estimated alongside and a 1-sided 97.5% upper confidence limit. The numerator for this calculation included all patients with confirmed inhibitors. The denominator was the sum of patients with confirmed inhibitors during the main phase of the trial and the completers of the main phase without confirmed inhibitors. The analyses evaluated relationships between the incidence rate of inhibitors and different patients and treatment characteristics.
- The incidence rates of FVIII inhibitors defined as inhibitor titres ≥0.6 BU for the extension part of trial and for the combined main and extension phases of the trial were also calculated. These rates were analysed in a similar way as the primary endpoint.
- The time to inhibitor development for all patients with inhibitors and for patients with high-titre inhibitors across main phase and extension phase of the trial was summarised using Kaplan-Meier plots.
- All AEs and SAEs were analysed for the main phase, the extension phase, the inhibitor cohort and the combined main and extension phases of the trial. The events were summarised by frequency of events and frequency of patients with any event.
- The incidence rates of high-titre inhibitors (≥5 BU) and clinically relevant inhibitors (≥0.6 BU with decreased recovery [<66% of expected level]) were calculated for the main, extension and combined main and extension phases of the trial. The 1-sided 97.5% upper confidence limits were provided for these calculations based on an exact calculation for a binomial distribution.

Results

Recruitment/ Number analysed

As of the data cut-off date (27 June 2018) for the report, 58 patients had completed the main phase of the trial and 49 patients had entered the extension phase, including 17 patients with inhibitors and 32 patients without inhibitors. In 2 inhibitor patients, the inhibitor was detected during the extension phase, and 1 of these 2 patients had a re-occurrence of inhibitor. The overall count of 26 inhibitors occurrences was comprised of 25 occurrences from the main phase and 1 occurrence from the extension phase. Overall, 48 patients completed both the main and extension phases of the trial and 1 patient completed the inhibitor cohort (and the trial) without entering the extension phase (Figure 2). One inhibitor patient successfully completed the inhibitor cohort with ITI treatment after developing an inhibitor during the main phase. This patient entered the extension phase but then restarted ITI treatment due to recurrence of inhibitor. Two (2) patients withdrew from the main phase with a reason stated as ‘other’. For both of these patients, their legal guardian requested a treatment change. Five (5) patients withdrew from the inhibitor cohort (2 patients due to adverse events (AEs), 2 patients due to withdrawal criteria no. 8 and 1 patient due to withdrawal criteria no. 6) and 1 patient withdrew from the extension phase due to withdrawal criterion no. 3.

As from the study protocol, a patient had to be withdrawn if the following applies:

1. Allergy/Anaphylaxis to the trial product

2. Treatment with FVIII products other than turoctocog alfa

3. Not in use: For inhibitor patients – inhibitor treatment failure with N8 treatment

4. Inhibitor treatment has not been started within 6 months from the date of confirmation of positive FVIII inhibitor (≥0.6 BU)

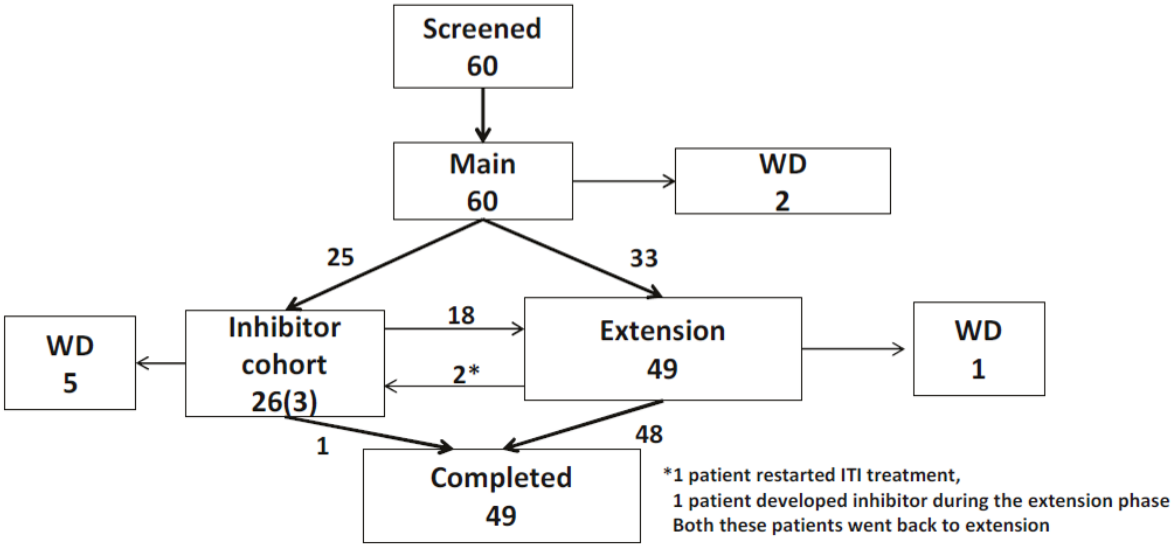
5. FVIII inhibitor titer decline from peak level is less than 20% after 12 months of inhibitor treatment

6. FVIII inhibitor is positive (≥0.6 BU) after 24 months of inhibitor treatment.

7. After completed inhibitor treatment (maximum 24 months), preventive treatment as described in the protocol is not resumed/started.

8. Preventive treatment not initiated at the patient's age of 24 months.

Figure 2: Patient flow chart



Numbers in the boxes are 'unique' patients, whereas numbers on the arrows are individual occurrences. Numbers in parenthesis refer to the number of patients remaining as of the data cut-off date 27 June 2018.

Baseline data

The trial population of male patients with severe haemophilia A (mean FVIII activity of 0.5%, ranging from 0.0 to 1.0%) was divided into 2 cohorts based on whether a patient developed an FVIII inhibitor during the trial.

Demography and baseline characteristics are summarised below.

Table 1: Baseline demographics – summary – full analysis set

	RFVIII (N8)		
	Inhibitor patients	Non inhibitor patients	Total
Number of patients	26	34	60
Age at baseline (months)			
N	26	34	60
Mean (SD)	10.5 (8.86)	10.0 (7.16)	10.2 (7.88)
Median	10.5	9.0	9.0
Min ; Max	0.0 ; 38.0	1.0 ; 42.0	0.0 ; 42.0
Ethnicity, N (%)			
N	26 (100.0)	34 (100.0)	60 (100.0)
Hispanic or Latino	1 (4.0)	4 (11.8)	5 (8.5)
Not Hispanic or Latino	25 (96.2)	30 (88.2)	54 (91.7)
Race, N (%)			
N	26 (100.0)	34 (100.0)	60 (100.0)
White	17 (65.4)	27 (79.4)	44 (73.3)
Black or African American	-	-	-
Asian	7 (26.9)	5 (14.7)	12 (20.0)
American Indian or Alaska Native	-	-	-
Native Hawaiian or Other Pacific Islander	-	-	-
Other	2 (7.7)	2 (5.9)	4 (6.7)
Genotype			
Type of mutation, N (%)			
N	25 (100.0)	32 (100.0)	57 (100.0)
Substitution	1 (4.0)	11 (34.4)	12 (21.1)
Splice Site Mutation	-	2 (6.3)	2 (3.5)
Deletions	5 (20.0)	5 (15.6)	10 (17.5)
Insertions	-	1 (3.1)	1 (1.8)
Duplication	1 (4.0)	4 (12.5)	5 (8.8)
Inversions	18 (72.0)	9 (28.1)	27 (47.4)
Translocation	-	-	-
Other	-	-	-
Genotype submutation, N (%)			
N	25 (100.0)	30 (100.0)	55 (100.0)
Substitution: Missense Mutations	-	7 (23.3)	7 (12.7)
Nonsense Mutations	1 (4.0)	4 (13.3)	5 (9.1)
Deletions: Large Deletion	1 (4.0)	1 (3.3)	2 (3.6)
Small Deletion	4 (16.0)	4 (13.3)	8 (14.5)
Insertions: Large Insertion	-	1 (3.3)	1 (1.8)
Small Insertion	-	1 (3.3)	1 (1.8)
Duplications: Large Duplication	1 (4.0)	-	1 (1.8)
Small Duplication	-	1 (3.3)	1 (1.8)
Other: Frameshift	-	2 (6.7)	2 (3.6)
Inversions: Intron 22	15 (60.0)	9 (30.0)	24 (43.6)
Intron 1	3 (12.0)	-	3 (5.5)
Family history of haemophilia, N (%)			
N	26 (100.0)	34 (100.0)	60 (100.0)
Yes	13 (50.0)	14 (41.2)	27 (45.0)
No	13 (50.0)	20 (58.8)	33 (55.0)
Family history of inhibitor, N (%)			
N	13 (100.0)	14 (100.0)	26 (100.0)
Yes	1 (7.7)	4 (28.6)	5 (18.5)
No	5 (38.5)	6 (42.9)	11 (38.5)
Unknown	7 (53.8)	4 (28.6)	11 (40.7)

Once patients developed FVIII inhibitors during the trial they were marked as inhibitor patients for the entire trial.

Efficacy results

Main and extension phases

1. A total of 60 patients were exposed to turoctocog alfa during the trial. The 59 patients (98.3%) that were administered a preventive regimen had a mean of 167.7 ED and received a mean of 172.4 injections per patient. In the inhibitor cohort, 26 inhibitor patients had an average of 246.7 ED to turoctocog alfa and received an average of 341.2 injections per patient.
2. Overall, 402 treatment-requiring bleeds were reported in 52 of 59 patients treated under 94.27 years of preventive regimen during the main and extension phases of the trial. Of these 402 bleeds, 133 bleeds occurred in 38 of 58 (65.5%) patients during the main phase and 269 bleeds in 40 of 49 (81.6%) patients during the extension phase.

3. A total of 98 bleeds occurred in 36 of 51 (70.6%) patients during on-demand treatment. Subcutaneous bleeds accounted for more than half (53.7%) of bleeds in patients during preventive treatment: 51.1% of bleeds in the main phase and 55.0% of those in the extension phase. Joint bleeds counted for 19.7% of all bleeds in patients during preventive treatment (10.5% of bleeds in the main phase and 24.2% of those in the extension phase).
4. During preventive regimen patients had an estimated ABR of 4.26 bleeds/patient/year (95% CI: 3.34−5.44), with 5.63 bleeds/patient/year in the main phase and 3.81 bleeds/patient/year in the extension phase.
5. Haemostatic response was rated as 'excellent' for 244 (60.7%) of the bleeds, 'good' for 102 (25.4%) of the bleeds, 'moderate' for 43 (10.7%) of the bleeds, and' none' for 2 (0.5%) of the bleeds in patients treated with preventive regimen across the main and extension phases.
6. The success rate for treatment of bleeds during a preventive regimen was 86.1% for 402 bleeds in the main and extension phase, and 84.2% for 133 bleeds in the main phase (including missing evaluations as failures). The success rates for the treatment of traumatic and spontaneous bleeds were 85.7% and 87.9%, respectively in patients receiving preventive treatment.
7. A total of 318 (79.1%) of bleeds reported for patients on preventive treatment were stopped with 1-2 injections of turoctocog alfa (227 [56.5%] bleeds stopped with 1 injection, 91 [22.6%] stopped with 2 injections and 30 [7.5%] stopped with 3 injections). The proportion of bleeds stopped with 1-2 injection was 87.9% in the main phase and 74.7%, in the extension phase.
8. Most of the patients on preventive treatment were treated with low-frequency prophylaxis i.e. with turoctocog alfa injections once or twice weekly.
9. Overall, patients on preventive treatment consumed a mean 5245.9 IU/kg of turoctocog alfa per patient per year. The mean monthly consumption of turoctocog alfa per patient was 437.2 IU/kg overall for patients on preventive treatment and 117.6 IU/kg for patients treated on demand. Patients treated preventively vs. those on demand received similar amounts of turoctocog alfa for treatment of a bleed from start to stop: 98.9 IU/kg vs. 86.1 IU/kg, respectively.
10. During the main and extension phases, a total of 51 caregivers or parents of the patients (with and without inhibitor) on preventive treatment missed an average of 2.8 days/patient/year (mean, range 0.0 – 94.7) from workplace due to a bleed. An average of 0.37 days/patient/year (mean, range 0.0 – 5.52) were missed by a total of 29 caregivers or parents of non-inhibitor patients on preventive treatment. More than half of patients received treatment for their severe bleed in a haemophilia clinic (55.6% of patients treated preventatively and 61.5% of those treated on demand).
11. Consistently, low scores of the HEMO-Sat questionnaire were recorded across domains at all visits (0 – 100, low score= good satisfaction). These low scores indicated a good treatment satisfaction across all domains.

Inhibitor cohort

1. In the inhibitor cohort, 179 bleeds were reported in 19 patients, of which most were classified as mild/moderate (95.5%) and caused by trauma (86.0%). The anatomical distribution of bleeds resembled that of the FAS with 54.7% of bleeds categorised as subcutaneous and 13.4% of bleeds categorised as "joint" by the location of bleeds. Half (50%) of the 8 severe bleeds reported were joint bleeds.
2. The inhibitor cohort exhibited a slightly higher estimated bleeding rate of 6.34 bleeds/patient/year (95% CI: 3.98−10.13), overall compared to all patients and non-inhibitor patients. However, the rate

decreased to 4.72 bleeds/patient/year (95% CI: 2.59–8.62) in the subset of 18 patients who completed the inhibitor cohort.

3. A total of 18 patients either completed or withdrew from ITI treatment. Of these 18 patients, 15 (83.3%) successfully completed ITI treatment with negative inhibitor.
4. In the inhibitor cohort, patients consumed a mean 1822.6 IU/kg/month/patient of turoctocog alfa, driven mostly by consumption during ITI treatment (2712.6 IU/kg/month/patient).
5. Caregivers or parents of patients with inhibitors missed on average more work days per year due to their child's bleeds during the inhibitor cohort compared to caregivers or parents of non-inhibitor patients on preventive treatment (mean 3.25 days/patient/year vs. mean 0.37 days/patient/year).

Safety results

1. A total of 26 patients had at least one occurrence of FVIII inhibitor across the whole trial following the exposure to turoctocog alfa (25/58 [43.1%] patients during the main phase and 1/33 [3.0%] patients during the extension phase). Of the 25 patients with inhibitors during the main phase, 1 patient had recurrence of inhibitor during the extension phase and restarted in inhibitor cohort, but data related to this re-occurrence was only listed to preserve statistical independence of summarized records and the occurrence itself was not counted in the estimate of the incidence rates.
2. Of the 26 inhibitor patients, 16 (61.5%) patients developed high-titre inhibitors (defined as a peak titre ≥5 BU) with a median (IQR) of 28.4 (48.2) BU.
3. High risk gene mutations (inversions, nonsense mutations and large deletions, and small deletions/insertions not located at or near adenine stretches) were identified in 34 patients. Of these, 19 patients (55.9%, p=0.049) developed FVIII inhibitors in the main phase. Of 19 inhibitor patients, 13 patients presented with high-titre inhibitors. Asian race had numerical increase in the risk as more Asians (58.3%) developed inhibitors than Whites (39.5%). However, this result was not statistically significant.
4. The FVIII gene mutation type after high-/low-risk reclassification was also statistically significant as a predictor for FVIII inhibitor development in main phase (p=0.003), resulting in 56.1% of the patients with high risk mutation and 6.7% of those with low risk mutation to develop FVIII inhibitors during the main phase. Conversely, 92.0% (n = 23) of the patients who developed inhibitor in the main phase had high risk mutations and only 4.0% (n = 1) had a low risk mutation according to this reclassification.
5. Patients who completed the inhibitor cohort had a median (IQR) time to first negative inhibitor test (<0.6 BU) of 127.5 (126.0) calendar days from when the inhibitor was detected.
6. There were 721 AEs reported in 57 (95.01%) patients over a total of 140.14 patient years, corresponding to an AE rate of 5.14 events per patient years of exposure.
7. The most frequently reported AEs were pyrexia (0.64 events per patient years of exposure), upper respiratory tract infection (0.47 events per patient years of exposure), nasopharyngitis (0.26 events per patient years of exposure) and FVIII inhibition (0.22 events per patient years of exposure).
8. A total of 46 AEs in 33 patients were judged by the investigator to be possibly or probably related to turoctocog alfa. Of these 46 AEs, 31 AEs were related to FVIII inhibition.

9. The trial reported 102 SAEs in 36 patients of which 27 SAEs in 25 patients were related to FVIII inhibition. The SAE rate was higher in the inhibitor cohort compared to the main phase i.e., 1.54 vs. 1.02 events per patient years of exposure, respectively. Several patients undergoing ITI treatment in the inhibitor cohort had procedure-related complications.

10. There were no cases of hypersensitivity related to turoctocog alfa. There were 2 cases of rashes during the main phase and both events were of short duration. Investigators considered these cases of rash as possibly related to trial product.

11. Laboratory parameter assessments and other safety-related examinations did not indicate clinically significant changes as a result of turoctocog alfa administration.

2.3.2. Discussion on clinical aspects

In accordance with their PIP (EMEA-000428-PIP-01-08-MO3) the MAH of NovoEight (Turoctocog alfa) submitted the final study report of the completed paediatric study NN7008-3809, a clinical Phase 3 trial evaluating the safety and efficacy of the B-domain truncated rFVIII in the prevention and treatment of bleeding episodes in PUPs with severe Haemophilia A without inhibitors. Turoctocog alfa is authorised for usage in all age groups.

A total of 60 patients were enrolled and exposed to turoctocog alfa, the mean age was 10.2 months, 73.3% of the subjects where White and 20% of Asian race. The primary safety endpoint was the incidence rate of FVIII inhibitors (≥0.6 BU) evaluated for the main phase of the trial. 25 out of 58 subjects (43.1%) completing the main phase developed FVIII inhibitory antibodies. Including one inhibitor patient from the extension phase, a total of 26 out of 58 patients had an inhibitor (44.8%). The total portion of patients with high titer inhibitors (≥5 BU) was 27.6% (which relates to more than half of all inhibitor patients) in the main phase and in total. It is considered that the observed inhibitor rate for turocotocog alfa is at the upper section amongst reported frequencies for various factor VIII products including recombinant variants, which are typically ranging around 25-30%. However, a conclusion whether the overall observed inhibitor rate and the relative fraction of high-titer inhibitor patients is unusual high is not possible due to methodological limitations with further reference made to the Factor VIII Art. 31 referral (EMA/765710/2017, EMA/763977/2017). As noted in the referral and as applicable for study NN7008-3809, the results are not considered sufficiently robust to allow a definite conclusion on the inhibitor risk for this product and therefore should not be reflected in the product information. The current SmPC of NovoEight includes a warning on the clinical importance of monitoring patients for FVIII inhibitor development within section 4.4. Furthermore, the tabled frequency of FVIII inhibition for PUPs is outlined as ‘very common’ in line with the referral and data of study NN7008-3809.

Within the preventive treatment regimen, patients had a mean of 167.7 EDs, an ABR estimated by Poisson modelling of 4.26 (5.63 in the main study phase and 3.81 in the extension phase), and a mean total consumption of 5245.9 IU/kg of turoctocog alfa per patient per year. During the on-demand treatment period patients exhibited a similar ABR of 4.27 bleeds/patient/year. A subanalysis of patients within the preventive regimen by dosing frequency has been provided, however, no definite conclusions can be drawn with regard to treatment frequency. As per current SmPC, dosing every second day or 3 times weekly is recommended in the paediatric population with recommended doses ranging between 25 - 60 IU/kg. Based on study NN7008-3809 data, no changes are required in this regard.

With reference made to secondary safety data and adverse events with possible or probable relation to turocotocog alfa, reported data were in line with the SmPC. A substantial amount of reported SAE were considered to be related to inhibitor development. Inhibitor patients on ITI also had increased rates of (catheter-related) infections. Noteworthy, 2 SAE of intracranial bleeds have been reported, however,

these were considered unlikely related to turoctocog alfa treatment. Narratives have been provided and the conclusion drawn from these can be followed.

Overall, it is considered that presented data of turoctocog alfa use in PUPs for prophylaxis, on-demand and for ITI do not change the overall benefit-risk assessment and are in line with the SmPC.

CHMP's overall conclusion and recommendation

In conclusion, results from the study NN7008-3809 investigating safety and efficacy of preventive and on-demand treatment with turoctocog alfa in haemophilia A PUPs showed a substantial rate of inhibitor development. However, this issue is sufficiently covered within the SmPC with reference made to the EMA Factor VIII Art. 31 referral. No further safety issues have bene identified that would imply changes of the SmPC. Efficacy in the treatment of bleeding episodes has been be demonstrated and data provided for prophylactic use are in line with SmPC recommendations. Thus, no further regulatory actions are required.

☒ **Fulfilled:**

No regulatory action required.

3. Additional clarification requested

None

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

NA

Clinical studies

Study title	Study number	Date of completion	Date of submission of final study report
A Multi-Centre, Multi-National, Open-Label Sequential Trial Comparing Pharmacokinetics and Safety of N8 and Advate in Subjects with Haemophilia A	NN7008-3522	LPLV: 01-October-2009	15 October 2012
A Multi-Centre, Open-Label, Non-Controlled Trial on Safety and Efficacy of N8 in Prevention and Treatment of Bleeds in Previously Treated Subjects with Haemophilia ASub-Trial:Safety and Efficacy of N8 in Prevention and Treatment of Bleeding during Surgical Procedures in Subjects with Haemophilia A	NN7008-3543	LPLV: 21-September-2011	15 October 2012
A Multi-Centre, Open-Label, Non-controlled Trial on Safety and Efficacy of N8 in Previously treated Paediatric Patients with Haemophilia A	NN7008-3545	LPLV: 21-November-2011	15 October 2012
Safety and Efficacy of turoctocog alfa in Prevention and Treatment of Bleeds in Paediatric Previously Untreated Patients with Haemophilia A	NN7008-3809	LPLV: 30 -June 2018. Three ITI patients still ongoing until December 2018	28-December-2018