14 November 2019
EMA/689155/2019
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/P46/009

Note

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

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1. Introduction

On 08 June 2019, the MAH submitted a completed paediatric study for NovoEight, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study NN7008-4028 is part of their clinical development program. However, it has not been listed in the Annex to Module 2 (*Annex. Line listing of all the studies included in the development program*).

NN7008-4028:
Efficacy and Safety of turoctocog alfa for Prophylaxis and Treatment of Bleeding Episodes in Previously Treated Chinese Patients with Haemophilia A

Submission of the NovoEight Guardian 7 NN7008-4028 Clinical Trial Report is a Stand-alone PAM (P46). The trial looked at the efficacy and safety of turoctocog alfa for the prevention and treatment of bleeds in previously treated Chinese patients with Haemophilia A. It included paediatric patients.

2.2. Information on the pharmaceutical formulation used in the study

The trial product, turoctocog alfa (NovoEight), was supplied as a sterile, freeze-dried powder in single-use vials of 500 IU/vial and 2000 IU/vial to be reconstituted with 4.3 mL of 0.9% sodium chloride for injection provided in prefilled syringes. Turoctocog alfa was administered as i.v. injection.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final clinical trial report in the frame of an article 46 procedure to fulfil the requirement of the Paediatric Regulation for submitting information on studies conducted in children within six months of completion.

2.3.2. Clinical study (according to the MAH)

Clinical study number and title

Study number: NN7008-4028 (EudraCT 2013-004791-35)

Title: Efficacy and Safety of turoctocog alfa for Prophylaxis and Treatment of Bleeding Episodes in Previously Treated Chinese Patients with Haemophilia A

PIP number: EMEA-000428-PIP01-08-M03

Description

The trial was conducted as part of the phase 3 development programme for turoctocog alfa, to investigate the efficacy and safety of the drug for prophylaxis and treatment of bleeding episodes in previously treated Chinese patients with haemophilia A.

The trial was conducted at 10 sites in 1 country (mainland China). Initiation date was 12Dec16, primary completion date was 16Mar18, and global completion date was 12Dec18.

Data cut-off was 15May19. Date of the report is 03Jun19.

Methods

Objective(s)

Primary objective:

- To evaluate the clinical efficacy of turoctocog alfa in treatment of bleeding episodes in Chinese patients with severe haemophilia A (FVIII ≤1%)

Secondary objectives:

- To assess the safety of turoctocog alfa in terms of immunogenicity
- To evaluate the clinical efficacy of turoctocog alfa during prophylaxis treatment
- To evaluate the consumption of turoctocog alfa during prophylaxis treatment and treatment of bleeding episodes
- PK phase only: To investigate the pharmacokinetic (PK) characteristics of turoctocog alfa after single dose injection
- Surgery only: To evaluate the efficacy and safety of turoctocog alfa during surgical procedures
- To evaluate impact of turoctocog alfa treatment on patient's health related quality of life (HRQOL

Study design

This was a single-country, multi-centre, open-label and non-randomised trial investigating the efficacy and safety of turoctocog alfa in previously treated Chinese males from 0 years with severe haemophilia A (FVIII ≤1%) living in mainland China.

The trial consisted of a main phase and an extension phase. In addition, a minimum of 12 and a maximum of 18 patients were to be enrolled in a PK session. This final report describes the trial results at the end of main phase visit.

Patients were administered turoctocog alfa i.v. as prophylaxis every second day or 3 times weekly, or as on-demand for the treatment of bleeds when necessary, and at the discretion of the investigator. In the main phase, switching between regimens was not permitted unless a patient developed low-titer FVIII inhibitors;

however, adjustment of the dose and dosing frequency was allowed. Once in the extension phase, patients had the option of switching from on-demand to prophylaxis at will. Patients could undergo surgery at any time during the trial as long as turoctocog alfa was used on and/or treatment of bleeds. The protocol specified that the maximum dose of turoctocog alfa per injection should not exceed 100 IU/kg BW.

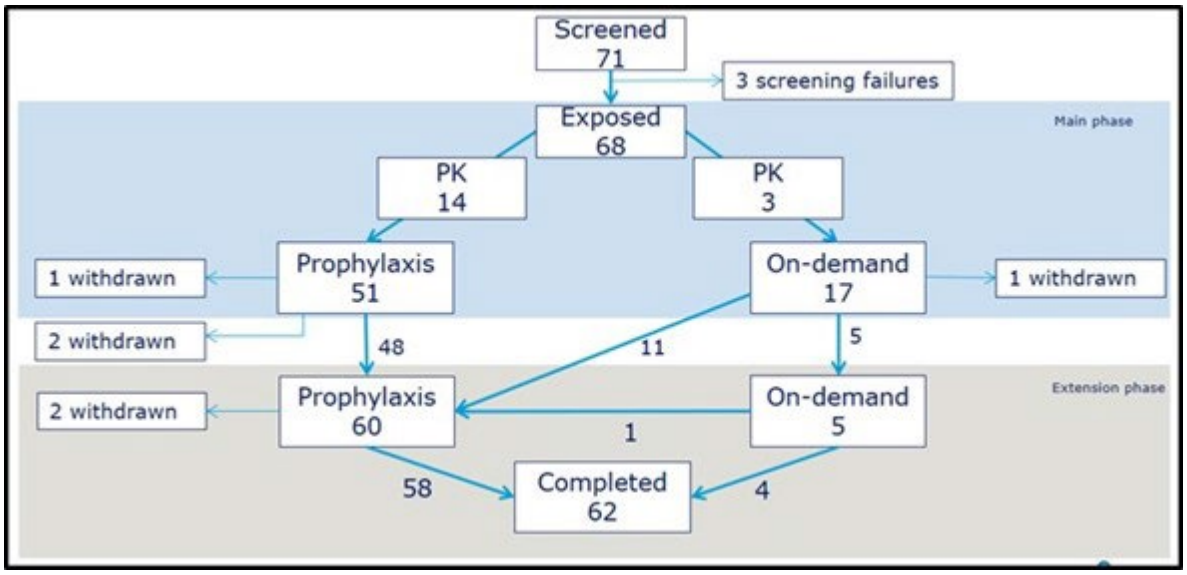
Study population /Sample size

A sample size of 60 patients was considered as sufficient to evaluate the safety and efficacy of turoctocog alfa. A total of 71 patients were screened; 3 patients were screening failures. The remaining 68 patients (full analysis set) received at least one dose of turoctocog alfa.

Of the 68 patients exposed to treatment, 51 patients started the main phase in a prophylaxis regimen while 17 patients initiated the trial with on-demand treatment. Two (2) patients (one from each regimen) withdrew at will from the main phase; the remaining 66 patients completed the main phase of the trial period.

A total of 17 patients were included in the PK assessment during the main phase.

Of the 66 main-phase completers, 2 patients in the prophylaxis regimen withdrew before starting the extension phase. Of the 64 patients who initiated the extension phase, 59 patients started the extension phase in a prophylaxis regimen while 5 patients started the extension phase in an on-demand regimen. Of these 5 patients, 1 patient later switched to a prophylaxis regimen Two (2) patients withdrew during the extension phase and the remaining 62 patients completed the extension period (for participant flow, see figure, below)



Treatments

Patients in the PK session were administered a single dose of 50 ±5 IU/kg BW turoctocog alfa followed by blood sampling for PK evaluation over a maximum of 3 days dependent on age.

In the prophylaxis regimen the recommended starting dose was 30 IU/kg for children <12 years and 25 IU/kg for adolescents and adults ≥12 years. Prophylaxis doses specified in the protocol ranged from 25−50

IU/kg BW (once every second day) or 25−60 IU/kg BW (3 times weekly) for patients <12 years, and 20−40 IU/kg BW (every second day) or 20−50 IU/kg BW (3 times weekly) for patients ≥12 years.

Bleeds were treated with one or more turoctocog alfa i.v. bolus injections as determined by the investigator. The protocol provided the following guide for dosing during bleeding episodes:

Dose (IU) = weight (kg)*desired factor level (IU/dL)*0.5.

In surgery, the investigator decided appropriate dosing and could refer to the following guidance in the protocol:

- Minor surgery (including tooth extraction): Maintain FVIII levels at 30−60 IU/dL and repeat dosing every 24 hours as needed until healing is achieved.
- Major surgery: Maintain FVIII levels at 80−100 IU/dL pre- and postoperatively by repeat injection every 8−24 hours until adequate wound healing, then adjust therapy for at least 7 more days to maintain FVIII levels at 30−60 IU/dL.

Batch numbers for turoctocog alfa were:

- 500 IU/vial: FR40415, FR40454 and GR40074
- 2000 IU/vial: FR40139, FR40248, FR40429 and GR40206

The planned duration of treatment was approximately 6 months per patient in the main phase, up to approximately 18 months in the extension phase which allowed both patients on prophylaxis and on-demand treatment. During the main phase some patients could also be included in a PK session.

Outcomes/endpoints

Pharmacokinetics:

The following PK parameters were assessed after a single dose of turoctocog alfa:

- Incremental recovery of FVIII
- Area under the curve (AUC0-inf)
- Half-life (t½)
- Clearance (CL)
- Highest measured FVIII activity in the profile (Cmax)

Efficacy:

Primary endpoint

Haemostatic effect of turoctocog alfa when used for treatment of bleeds, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) during the main phase (6 months duration per patient).

Supportive secondary efficacy endpoints

- Haemostatic effect of turoctocog alfa when used for treatment of bleeds, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) during the trial period of 24 months

- Number of bleeds (total bleeds assessed as annual bleeding rate) per patient during both the main phase of 6 months and during the trial period of 24 months
- Consumption of turoctocog alfa during both the main phase of 6 months and during the trial period of 24 months
    - Consumption of turoctocog alfa for bleeding treatment (average dose to treat a bleed, number of injections and IU/kg per bleed) during both the main phase of 6 months and during the trial period of 24 months
    - Consumption of turoctocog alfa during prophylaxis treatment (average prophylaxis dose and IU/kg per month and per year) per patient during both main phase of 6 months and during the trial period of 24 months
    - Total consumption of turoctocog alfa (IU/kg per month and per year) per patient during both the main phase of 6 months and during the trial period of 24 months.

Patient reported outcome endpoint

The following patient reported outcome (PRO) was evaluated: Change in total scores for reported health-related quality of life during both the main phase of 6 months and during the trial period of 24 months.

Safety:

Supportive secondary safety endpoints

- Incidence rate of inhibitory antibodies against FVIII (≥0.6 BU) during both, the main phase of 6 months and during the trial period of 24 months
- Adverse events (AEs) and serious adverse events (SAEs) reported during both, the main phase of 6 months and during the trial period of 24 months.

Surgery:

The following surgery endpoints were evaluated during both, the main phase of 6 months and during the trial period of 24 months:

- Haemostatic effect evaluated on the four-point scale (excellent, good, moderate and none) and assessed by the investigator/surgeon on the day of surgery (Day 1) and on the last day in the post-operative period the patient is at the trial/surgery site
- Loss of blood and requirements for transfusion on the day of surgery (Day 1) and during the post-operative period Days 2−7 or until the last day the patient is at the trial/surgery site whichever comes first
- AEs/SAEs occurred on the day of surgery (Day 1) and during the post-operative period Days 2−7 or until the last day the patient is at the trial/surgery site whichever comes first.

Statistical Methods

Evaluation of data was based mainly upon descriptive statistics, i.e. summary tables, listings, and figures. Categorical data was summarised by frequency tables while continuous data was summarised by mean, standard deviation, minimum and maximum value.

Definition of analysis sets

Both the 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

- **Primary endpoint**: The haemostatic effect of turoctocog alfa was summarised by age group and regimen in frequency tables containing counts and percentages and assessed on a predefined four-point scale: excellent, good, moderate and none. Data was presented separately for the main phase and the combined main and extension phases. Treatment responses rated good or excellent were counted as treatment successes while those judged moderate, none or documented 'missing' were accrued as treatment failures. The effect was also summarised by cause, site, and classification of bleed.
- The number of bleeds (total bleeds assessed as annual bleeding rate) per patient was presented by regimen for the main phase and the combined main and extension phases and included only treatment requiring bleeds. A further sensitivity analysis calculated the annualised bleeding rate for both treatment requiring and non- treatment requiring bleeds.
- The annualised bleeding rate (ABR) was analysed by a negative binomial model and presented with confidence intervals by trial phase and treatment regimen.
- Consumption of turoctocog alfa for treatment of bleeds (average dose to treat a bleed, number of injections and IU/kg per bleed) during the main phase and the combined main and extension phases was summarised and listed according to age, regimen, and total.
- Evaluation of PRO data was based on changes to HAEM-QoL scores (range 0−100) and the results were summarised and listed.

Safety

- The incidence rate of FVIII inhibitors (≥0.6 BU) presented as the percentage of patients developing FVIII inhibitors was calculated and a 1-sided 97.5% upper confidence limit provided based on an exact calculation for a binomial distribution. For the calculation of the incidence rate the numerator was to include all patients with FVIII inhibitors while the denominator was to include all patients in the trial exposed to turoctocog alfa.
- Frequency of AEs and SAEs reported during the main phase of 6 months and the combined main and extension phases were summarised by frequency of events and frequency of patients with any event. The statistical output provided summary tables of events by treatment period, age group, regimen and total events.

Pharmacokinetics

- This final report included the full PK evaluation with PK endpoints presented by the mean, standard deviation, minimum and maximum value, the geometric mean and 95% confidence interval for the geometric mean.

Surgery

- Where applicable, the investigator/surgeon evaluated haemostatic effect during surgery on the four-point scale (excellent, good, moderate and none) twice: on the day of surgery (Day 1) and on the last day in the post-operative period that the patient was at the trial/surgery site.
- The trial assessed loss of blood and requirement for transfusions on the day of surgery (Day 1) and during the operative period (Days 2−7) or until the last day the patient was at the trial/surgery site, whichever came first.

Results

Recruitment/ Number analysed

refer to Methods: study population

Baseline data

The trial population included Chinese males, 2 to 53 years of age with severe haemophilia A (FVIII ≤1%). The mean (SD) time the patients have had the diagnosis of haemophilia was 11.2 (10.4) years from the time to diagnosis increased with age as expected; the mean for smaller children being 2.8 and the mean for adults being 25.2 years.

In the 1 year prior to enrolment in the trial, a total of 40 patients were on prophylaxis at some time point, while a total of 32 patients were on-demand at some time point. The mean ABR during the 1 year prior to trial was 53.7 bleeds/patient/year for patients during on-demand regimen. Four (4) patients who switched between prophylaxis and on-demand counted in both places.

Pharmacokinetic

- PK was assessed in 17 patients (age 3 to 44 years).
- FVIII activity is available from both one-stage clotting assay and chromogenic assay. PK data based on the chromogenic assay are presented in text.
- The 17 patients evaluated had an overall incremental recovery (mean (SD) of 0.023 (0.006) (IU/mL)/(IU/kg). Incremental recovery was 0.022 (0.003), 0.026 (0.005) and 0.026 (0.004) (IU/mL)/(IU/kg), respectively, in small children, older children and adults.
- The incremental recovery mean (SD) in the 3 adolescent patients was 0.014 (0.007) (IU/mL)/(IU/kg).
- Dose normalised AUC0-inf appears high in adolescents, but when adjusted for the variation in sampling frequency by plotting on a logarithmic scale, the results were more consistent between small children and adults(68.9 and 69.4 IU*h/mL) and appears high in older children (70.5 IU*h/mL) and highest in adolescents (72.0 IU*h/mL).
- The half-life (t½) was similar in children <12 years and adults: mean (SD) t½ in small children, older children, adolescents and adults of 8.5 (1.4), 8.3 (3.1), 11.6 (0.6) and 8.4 (1.9) hours, respectively with an overall t½ of 9.0 (2.4) hours.
- The mean (SD) CL was same in older children and adults, slightly higher in children than adults and much higher in adolescents: 3.7 (0.9) mL/h/kg (small children), 3.5 (1.2) mL/h/kg (older children) and 3.5 (0.3) mL/h/kg in adults. Adolescents had a CL of 5.5 (2.2) mL/h/kg.
- Mean Cmax (SD) was 1.2 (0.2) IU/mL in small children, 1.4 (0.3) IU/mL in older children, 0.9 (0.5) IU/mL in adolescents, and 1.6 (0.2) IU/mL in adults. The overall mean Cmax (SD) was 1.3 (0.3) IU/mL.

Efficacy results

- A total of 611 bleeds were reported in 47 patients during the main phase including 48 bleeds in 6 small children, 245 bleeds in 20 older children, 28 bleeds in 6 adolescents and 290 bleeds in 15 adults. Joint bleeds (including multiple location bleeds) (445 bleeds) accounted for most of these bleeds in older children (68.6% of bleeds), adolescents (96.4% of bleeds) and adults (81.0% of bleeds).
- A total of 925 bleeds were reported in 54 patients during the main plus extension phase including 65 bleeds in 7 small children, 405 bleeds in 24 older children, 53 bleeds in 8 adolescents and 402 bleeds in 15 adults. Joint bleeds (including multiple location bleeds) (650) accounted for most of these bleeds in older children (64.2% of bleeds), adolescents (92.5% of bleeds) and adults (80.1% of bleeds). Most bleeds in small children were subcutaneous (43.08%) or occurred in joints (29.23%).
- A total of 50.4% of the bleeds in the prophylactic regimen during the combined main plus extension phase occurred spontaneously. Adolescents reported a higher rate of spontaneous bleeds (71.4%) during prophylaxis *versus* the other age groups: 87.2% of bleeds were spontaneous in the main phase and 83.4% of bleeds were spontaneous in the combined main plus extension phases.
- Haemostatic response was successful (rated good or excellent) in 95.1% of the 611 treated bleeds in the main phase (primary endpoint). It was 95.9% and 95.4% in the extension phase and main plus extension phases, respectively.
- The haemostatic success was 91.8% in prophylaxis and 96.5% in on-demand regimen main plus extension phase. It exceeded 90% in the majority of cases regardless of subgroups (treatment, age group, bleed location or treatment period) when counting missing values as treatment failures.
- Similar proportions of the 148 traumatic and 771 spontaneous bleeds in the main plus extension phase had successful haemostatic responses (93.2% and 95.8%, respectively).
- 872 of the total 925 (94.3%) bleeds in the trial were stopped with 1-2 injections of turoctocog alfa.
- The estimated ABR in patients on prophylaxis was 4.7 bleeds/patient/year in the main phase and 2.9 bleeds/patient/year in the main plus extension phase, indicating a reduction in ABR over time. This development was most obvious in adult patients (10.7 bleeds/patient/year during main phase and 4.9 bleeds/patient/year during the main plus extension). The estimated ABR in on-demand patients (73.2 bleeds/patient/year during main phase and 71.1 bleeds/patient/year for the entire trial).
- Approximately half of the patients (52.0%) with target joints at baseline had no bleeds in those joints during prophylaxis treatment and 76.0% of patients on prophylaxis treatment had all baseline target joints resolved during the trial, overall suggesting a benefit of prophylaxis treatment to improve joint conditions.
- For the 48 patients who received only prophylaxis treatment in both the main and the extension phase, 60 target joints were reported at baseline in 35 patients. All baseline target joints were permanently resolved in 65.7% of the patients per protocol definition and in 91.4% of the patients when using the definition per ISTH.
- At the start of trial, the majority (90.20%) of prophylaxis patients in main phase and (90.48%) in main plus extension phase preferred dosing three times weekly, with no changes in frequency throughout the main phase.

- The average preventive dose was 40.5 IU/kg were similar to the mean preventive dose of turoctocog alfa in the prophylaxis regimen during the main, extension and main plus extension phase (39.6, 40.8 and 40.5 IU/kg BW). The mean total annual consumption when used for treatment were 6514, 6449 and 6475 IU/kg BW/year/patient. The mean total annual consumption for prevention were 6221, 6304 and 6228 IU/kg BW/year/patient.
- For the treatment of bleeds, prophylaxis patients in the main phase consumed a mean (SD) 20.49 (25.70) IU/kg BW/month/patient of turoctocog alfa and prophylaxis patients in the main plus extension phase consumed a mean (SD) 14.20 (20.55) IU/kg BW/month/patient of turoctocog alfa.
- A total of 7 patients underwent 10 surgeries; 3 patients had major surgeries and 5 patients had minor surgeries. Of the 10 surgeries, turoctocog alfa was used in only 8 surgeries and hence only 8 surgeries were assessed for efficacy. Haemostatic response to turoctocog alfa was successful (excellent and/or good) during and after all the 8 surgeries and none of the patients received a blood transfusion.
- HAEM-QOL scores improved with time at the end of main phase and at the end of trial across all age groups. Changes to scores from baseline to end of main phase were -6.8 and (children 8−12 years), -3.5 (adolescents 13−16 years) and -3.4 (adults ≥17 years). Changes to scores from baseline to end of trial were -10.1 (children 8−12 years), -4.9 (adolescents 13−16 years) and -6.3 (adults ≥17 years). A negative change reflected an improvement in quality-of-life related to haemophilia.
- For adults, QoL scores related to 'physical health,' 'feeling' and 'view of yourself' improved the most. Adolescents had the greatest HAEMO-QOL scores for 'physical health,' 'view of yourself' and 'perceived support.' Children saw the greatest decrease HAEMO-QOL scores in 'physical health,' 'view of yourself' and 'sports and school.'

Safety results

The following lists the main safety conclusions for the 3 treatment periods: main phase, extension phase and combined main plus extension phases.

- No patient developed FVIII inhibitors throughout the trial period.
- The total number of AEs (including surgeries) was 71 AEs reported in 35 patients (51.5%) at an event rate of 2.474 AEs/patient/year in the main phase and 143 AEs reported in 46 patients (67.6%) at an event rate of 1.435 AEs/patient /year in the main plus extension on exposure to turoctocog alfa.
- The total number of AEs (excluding surgeries) was 69 AEs reported in 35 patients (51.5%) at an event rate of 2.432 AEs/patient/year in the main phase and 138 AEs reported in 46 (67.6%) patients at an event rate of 1.390 AEs/patient/year in the main plus extension on exposure to turoctocog alfa.
- The total number of AEs during prophylaxis regimen (excluding surgeries) was 59 AEs reported for 29 patients (56.9%) at an event rate of 2.757 AEs/patient/year in the main phase and 123 AEs reported in 42 patients (66.7%) at an event rate of 1.386 AEs/patient/year in the main plus extension phase on exposure to turoctocog alfa.
- The total number of AEs during on-demand-regimen (excluding surgeries) was 10 AEs reported for 6 patients
- (35.3%) at an event rate of 1.434 AEs/patient/year in the main phase and 15 AEs reported for 7 patients (35.3%) at an event rate of 1.434 AEs/patient/year in the main phase and 15 AEs reported for

7 patients (41.2%) at an event rate of 1.422 AEs/patient/year in the main pluas extension phase on exposure to turoctocog alfa.

- AEs during main plus extension phase reported in ≥5% of patients included upper respiratory tract infections (27.9% of patients), nasopharyngitis (14.7% of patients), diarrhoea (7.4% of patients) and pyrexia (8.8% of patients) with event rates of 0.272, 0.111, 0.050 and 0.091 AEs/patient years, respectively.
- The majority (≥99%) of AEs were of mild to moderates severity in both treatment periods.
- Five (5) AEs in 3 patients during surgeries (2 events of open wound of scalp; 1 event of peripheral neuralgia, loose tooth and tetanus anti toxin allergy each) were reported. All events were considered non-serious, judged to be unlikely related to turoctocog alfa by the investigator and resolved at the time of this report.
- There were 4 SAEs reported in 3 patients (4.4% of the trial population) in the prophylaxis regimen during the main phase (femur fracture in the first patient and lung infection and asthma in the second patient). All events were unlikely related to turoctocog alfa by the investigator and resolved at the time of this report.
- There were no AEs leading to withdrawal and no patients died in the trial.

2.3.3. Discussion on clinical aspects (Assessment)

Overall, design and results of the presented study do not raise concerns regarding safety and efficacy in the paediatric population. No amendments of the SmPC are considered to be necessary. However, the Critical Overview Statement should focus on paediatric evaluation and present age-related results.

Pharmacokinetics:

According to the protocol, single dose for PK-evaluation was 50 ± 5 IU/kg. Of note, all documented doses have been above 50 IU/kg for all age-groups. The Clinical Guideline1 suggests 25-50 IU/kg. Results should be understood in this context. Sampling schedule for adults (0'', 15'', 30'', 1', 4', 8', 12', 24', 30', 48') and reduced for all children 0-11 (0'', 30'', 1', 24') has been adapted from the suggestion of the Clinical Guideline (0'', 15'', 30'', 1', 3', 6', 9', 24', 28', 32', optional 48'). Overall, patient-numbers are low in the paediatric subgroups. The following summary table has been provided within the CSR:

Table 11-13 PK parameters by age group, chromogenic assay - full analysis set excluding outliers

PK Endpoints	Small Children (0 -<6 years)		Older Children (6 -<12 years)		Adolescents (12 -<18 years)		Adults (>=18 years)		Total	
	Mean (SD)	Min; Max	Mean (SD)	Min; Max	Mean (SD)	Min; Max	Mean (SD)	Min; Max	Mean (SD)	Min; Max
N	4		6		3		4		17	
AUC_{0-inf} (IU*h/mL)	16.4 (3.5)	12.8; 19.8	17.7 (7.3)	9.5; 30.1	11.2 (4.7)	6.9; 16.1	16.9 (1.5)	15.5; 18.9	16.0 (5.3)	6.9; 30.1
Dose normalised AUC_{0-inf} log[1] (IU*h/mL)	68.9 (13.0)	57.8; 83.3	70.5 (28.4)	44.8; 118.4	72.0 (11.3)	61.4; 84.0	69.4 (10.3)	60.9; 81.6	70.2 (18.2)	44.8; (118.4)
$t_{1/2}$(h)	8.5 (1.4)	7.7; 10.1	8.3 (3.1)	5.7; 13.2	11.6 (0.6)	10.9; 12.1	8.4 (1.9)	6.8; 10.8	9.0 (2.4)	5.7; 13.2
Incremental Recovery (IU/mL)/(IU/kg)	0.022 (0.003)	0.019; 0.025	0.026 (0.005)	0.018; 0.031	0.014 (0.007)	0.007; 0.021	0.026 (0.004)	0.021; 0.030	0.023 (0.006)	0.007; 0.031
CL (mL/h/kg)	3.7 (0.9)	2.9; 4.7	3.5 (1.2)	1.9; 5.3	5.5(2.2)	3.3; 7.6	3.5 (0.3)	3.0; 3.7	3.9 (1.4)	1.9; 7.6
C_{max} (IU/mL)	1.2 (0.2)	1.0; 1.4	1.4 (0.3)	1.0; 1.7	0.9 (0.5)	0.4; 1.4	1.6 (0.2)	1.3;1.7	1.3 (0.3)	0.4; 1.7

N: Number of patients, AUC: Area under the curve, CL: Clearance, C_{max}: Maximal FVIII activity, $t_{½}$: Terminal half-life, SD: Standard deviation.

Note: For 1 small child the terminal rate constant could not be estimated, and therefore the AUC_{0-inf}, AUC_{0-inf} log and CL were not calculated.

[1]: Dose normalised $AUC_{(0-Inf)}$ log is the dose normalised area under the log10-transformed curve that lies above the -log10(LLOQ*0.5) horizontal line.

1Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products 26 July 2018 EMA/CHMP/BPWP/144533/2009 rev. 2

Similar Table should be available in the Overview (and EPAR). However, mean-values should be replaced by medians and range due to the low patient numbers, and doses should be amended - similar to the table, below (from Table 14.2.100 PK endpoints by age group, chromogenic assay – full analysis set):

Parameter median min;max	0-6y	6-12y	12-18y	Adult	Total
Number	4	6	3	4	17
Dose [IU/kg]	57.1 55.0;60.4	55.9 50.2;56.7	53.1 52.7;58.1	57.8 57.5;59.2	56.5 50.2;60.4
AUC [IU*h/ml]	14.9 10.6;17.1	14.4 9.4;26.9	9.1 6.5;15.2	14.2 13.4;16.4	14.2 6.5;26.9
Cl [ml/h/kg]	3.3 2.9;4.7	3.6 1.9;5.3	5.5 3.3;7.6	3.5 3.0;3.7	3.5 1.9;7.6
Incr Recovery [IU/dl/IU/kg]	2.1 1.9;2.5	2.6 1.8;3.1	1.5 0.7;2.1	2.6 2.1;3.0	2.3 0.7;3.1
Half-life [h]	7.7 7.7;10.1	7.3 5.7;13.2	11.8 10.9;12.1	8.0 6.8;10.8	8.7 5.7;13.2

From the presented data the adolescent age-group does not show conclusive PK-results. It is taken that the number of adolescents (3) in the PK-sub-study (overall 17 patients) was not representative.

Efficacy:

Primary efficacy endpoint was the haemostatic effect. This effect is presented in an age-related manner in Table 11-5 of the CSR:

Table 11-5 Haemostatic response when used for treatment of bleeds by age group, main phase - full analysis set

	Small children (0 - <6 years)	Older children (6 - <12 years)	Adolescents (12 - <18 years)	Adults (>= 18 years)	Total
Number of patients	9	33	11	15	68
Number of patients with bleeds*, N (%)	6 (66.7)	20 (60.6)	6 (54.5)	15 (100.0)	47 (69.1)
Number of bleeds*	48	245	28	290	611
Haemostatic response, N (%)					
N	48 (100.0)	245 (100.0)	28 (100.0)	290 (100.0)	611 (100.0)
Excellent	35 (72.9)	156 (63.7)	20 (71.4)	190 (65.5)	401 (65.6)
Good	12 (25.0)	73 (29.8)	8 (28.6)	87 (30.0)	180 (29.5)
Moderate	1 (2.1)	15 (6.1)	-	13 (4.5)	29 (4.7)
None	-	-	-	-	-
Missing	-	1 (0.4)	-	-	1 (0.2)
Success/failure (incl. missing as failure), N (%)					
N	48 (100.0)	245 (100.0)	28 (100.0)	290 (100.0)	611 (100.0)
Success	47 (97.9)	229 (93.5)	28 (100.0)	277 (95.5)	581 (95.1)
Failure	1 (2.1)	16 (6.5)	-	13 (4.5)	30 (4.9)
Success/failure, N (%)					
N	48 (100.0)	244 (100.0)	28 (100.0)	290 (100.0)	610 (100.0)
Success	47 (97.9)	229 (93.9)	28 (100.0)	277 (95.5)	581 (95.2)
Failure	1 (2.1)	15 (6.1)	-	13 (4.5)	29 (4.8)

Success is defined as either Excellent or Good. Failure is defined as either Moderate or None.
* Only bleeds treated with turoctocog alfa are included

It is acknowledged that the haemostatic effect is convincing for all paediatric age groups.

Annualized bleeding rate (ABR) is no standardized clinical endpoint: E.g. definition of a bleeding episode to be "counted" is not standardized but highly relevant, and the observational period should cover at least 1 year for such low numbers e.g. under prophylaxis and taking seasonal effects into account. If ABR is presented it should in general be correlated with respective compelling consumption data.

Consumption of factor concentrate reflects efficacy from a therapeutic point of view. This should cover consumption in IU/kg per year (month) for on-demand patients and for prophylaxis patients (including complete concentrate supply) relying on similarly adequate observational period. In addition, according to the Clinical Guideline, consumption per event (bleeding episode) is requested in IU/kg per episode. If available, it might be of interest to compare consumption for bleeding episodes while under prophylaxis and while in an on-demand regimen. Consumption – according to the Clinical Guideline - is expected to be reflected in the Critical Expert Overview and the EPAR in an age-related-manner.

Surgery

Haemostatic Efficacy in (major) 8 surgeries has been described. Dosage and duration of treatment follows the Core-SmPC. Age-related consumption of factor concentrate per kg and event (major surgery) should be reflected in the Critical Expert Overview.

Safety:

Relevant in the frame of this article 46-procedure is a comparison of the safety profiles of the respective paediatric age-groups and adults. This includes an analysis not only of numbers but also of type and relevance of the AE regarding FVIII replacement therapy. According to the CSR, the following (summary-) evaluation regarding treatment emergent AEs is available e.g. for the main plus extension phase:

- 'infections and infestations' (72 AEs reported in 33 patients; with upper respiratory tract infection cited more frequently)
- 'gastrointestinal disorders' (16 AEs reported in 13 patients; with diarrhoea cited more frequently)
- 'respiratory, thoracic and mediastinal disorders' (13 events reported in 10 patients; with cough (4 AEs) more frequent than oropharyngeal pain (3 AEs)
- 'general disorders and administration site conditions' (11 events reported in 8 patients; with pyrexia cited more frequently)
- 'skin and subcutaneous tissue disorder' (10 events reported in 8 patients; with dermatitis allergic acne, urticaria papular and urticaria cited more frequently)

Overall, there seems to be no additional signals regarding AE-reporting, overall. Tables are available in Section 14 of the CSR, presenting AEs age-group-related. However, respective analysis and assessment comparing age-groups and currently approved SmPC-wording is missing. AEs of special interest, e.g. hypersensitivity-related AEs, have not been presented.

3. Rapporteur's overall conclusion and recommendation

The submitted study report includes all paediatric age-groups and adults within 70 treated patients. Overall, data do not change the positive benefit-risk-assessment for the medicinal product. Currently available information in the SmPC regarding paediatric patients remains unchanged. However, adequate age-related presentation of results for PK, efficacy, surgery and safety in the Critical expert overview is missing.

☒ **Not fulfilled:** Based on the data submitted, the MAH should provide an update of the Critical Expert Overview as basis for the EPAR (see section "Request for Supplementary Information / RfSI").

4. Request for supplementary information (RfSI)

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

Update of the Critical Overview Document is requested. The update should present study-results in an age-related manner. Regarding Pharmacokinetics, age-related PK-data based upon median and range, and reflecting the applied dose, should be amended, including a well-arranged table. Regarding Efficacy – including surgery, the targets of the Clinical Guideline should be presented in an age-related manner, covering haemostatic efficacy and consumption of the factor concentrate as outlined in the assessment. Identified unexplained results from the adolescent age-group should be briefly reflected and commented. Similarly, safety should be amended by age-group-related analysis and assessment. AEs of special interest, e.g. hypersensitivity-related AEs, should be presented. Respective summarising statement regarding SmPC-update should be provided.

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

Assessment of the MAHs responses to RfSI

Question 1

Update of the Critical Overview Document is requested. The update should present study-results in an age-related manner. Regarding Pharmacokinetics, age-related PK-data based upon median and range, and reflecting the applied dose, should be amended, including a well-arranged table. Regarding Efficacy – including surgery, the targets of the Clinical Guideline should be presented in an age-related manner, covering haemostatic efficacy and consumption of the factor concentrate as outlined in the assessment. Identified unexplained results from the adolescent age-group should be briefly reflected and commented. Similarly, safety should be amended by age-group-related analysis and assessment. AEs of special interest, e.g. hypersensitivity-related AEs, should be presented. Respective summarising statement regarding SmPC-update should be provided.

MAH's responses

The MAH submitted an updated Critical Expert Overview.

Assessment of the MAH's responses

Submitted updated Critical Expert Overview presents age-related study-results and respective overall conclusion.

Conclusion

Issue is solved.

5. Rapporteur's overall conclusion on P46 009

The submitted study report includes all paediatric age-groups and adults within 70 treated patients. Overall, data do not change the positive benefit-risk-assessment for the medicinal product. Currently available information in the SmPC regarding paediatric patients remains unchanged. Adequate age-related presentation of results for PK, efficacy, surgery and safety in the Critical Expert Overview has been provided.

Study NN7008-4028 has been amended to the Annex to Module 2 (*Annex. Line listing of all the studies included in the development program*).

☒ Fulfilled - No further action required

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

Clinical studies

Product Name: NovoEight
Active substance: turoctocog alfa

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 turoctocog alfa and Advate in Subjects with Haemophilia A	NN7008-3522	01 October 2009	15 October 2012
A multi-centre, multinational, open-label, safety, efficacy, single-arm trial in patients with severe haemophilia A investigating turoctocog alfa when used for prevention and treatment of bleeds. The trial included a sub-trial designed to evaluate the safety and efficacy of turoctocog alfa when used for prevention and treatment of bleeding during surgical procedures and in the surgery period.	NN7008-3543	21 September 2011	15 October 2012
A multi-centre, open-label, non-controlled safety and efficacy trial of turoctocog alfa in previously treated paediatric patients with haemophilia A.	NN7008-3545	21 November 2011	15 October 2012
Safety and Efficacy of turoctocog alfa in Prevention and On-demand Treatment of Bleeding Episodes in Subjects with Haemophilia A	NN7008-3568	30 June 2016	28-December 2016
Safety and Efficacy of turoctocog alfa in Prevention and Treatment of Bleeds in Paediatric Previously Untreated Patients with Haemophilia A	NN7008-3809	30 June 2018 Three ITI patients still on-going until December 2018	28 December 2018