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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/P46/006

Note

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

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1. Introduction

On 28 December 2016, the MAH submitted the final study report for NovoEight clinical trial NN7008-3568, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended (eCTD 044). A short critical expert overview has been provided. No regulatory consequences have been identified by the MAH.

NOTE: The trial product, turoctocog alfa, was previously named N8. The name was changed to turoctocog alfa after finalisation of the protocol for this trial.

Scientific discussion

1.1. Information on the development program

Study no. NN7008-3568, evaluating safety and efficacy of turoctocog alfa in prevention and on demand treatment of bleeding episodes in subjects with haemophilia A, is part of the turoctocog alfa clinical development program. A line listing of all the concerned studies is annexed.

1.2. 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 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. It was recommended to use turoctocog alfa immediately after reconstitution. Exposure to direct sunlight and/or freezing was to be avoided.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final report for study no. NN7008-3568 to assess safety and efficacy of turoctocog alfa in prevention and on demand treatment of bleeding episodes in subjects with haemophilia A.

1.3.2. Clinical study

Description

Objectives (for main trial and on-demand sub-trial)

Primary objective:

- To assess the safety of turoctocog alfa for prevention (only applicable for subjects in the preventive regimen) and treatment of bleeds.

Secondary objective:

- To assess the efficacy of turoctocog alfa for prevention (only applicable for subjects in the preventive regimen) and treatment of bleeds.
- To assess Patient Reported Outcomes over time (only for applicable subjects).

With Amendment 17 to the protocol, two new treatment regimens were added - once every third day and twice weekly regimens in order to investigate the effect of less frequent than the standard prophylaxis dosing on annualised bleeding rates.

Primary objective for the surgery sub-trial:

- To evaluate the efficacy of turoctocog alfa in surgery.

Secondary objectives for the surgery sub-trial:

- With Amendment 1, this objective was added: To evaluate the haemostatic response to turoctocog alfa in the postsurgery period.
- To evaluate the safety of turoctocog alfa in surgery.

With Amendment 17, a PK sub-trial in subjects with high BMI was added.

Primary objective for the PK sub-trial:

- To investigate single dose pharmacokinetics in patients with BMI $\geq$30 kg/m^2

Study design

The NN7008-3568 trial was designed as a non-randomised, open-label, multi-national, single treatment arm, safety and efficacy extension trial wherein patients completing one of the trials NN7008-3543, NN7008-3545, NN7008-3600, NN7008-3893 and N7008-4015 could continue treatment with turoctocog alfa. In this trial, long-term safety and efficacy of turoctocog alfa in patients with hemophilia A without inhibitors and a FVIII activity ≤1% were evaluated. Furthermore, a surgery sub-trial was designed to provide information on efficacy and safety of turoctocog alfa administered as either bolus or continuous infusion during surgery. All patients had the possibility to undergo major and minor surgery as part of the surgery sub-trial if the surgical intervention required at least 7 days of turoctocog alfa surgery related treatment including the day of surgery. An on-demand sub-trial was added to ensure collection of data in patients in an on-demand regimen. In addition, a pharmacokinetic sub-trial investigating the pharmacokinetics in patients with BMI $\geq$30 kg/m^2 was added. Eligible patients were to be administered a single dose of turoctocog alfa (50 IU/kg) followed by blood sampling for PK evaluation.

Study population /Sample size

For sample size considerations see statistical methods section.

Inclusion criteria for the main trial:

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 subject).

2. Completion of the pivotal trial (NN7008-3543), paediatric trial (NN7008-3545), Japanese trial (NN7008-3600), PK trial (NN7008-3893), PK trial (NN7008-4015) or on demand sub-trial in the Extension trial (NN7008-3568).

Inclusion criteria for new subjects starting in the 6 months on-demand sub-trial:

1. Informed consent obtained prior to any trial-related activities.

2. Male subjects with the diagnosis of severe (FVIII ≤1%) haemophilia A from age 18 to 70 years.

3. Documented history of at least 150 exposure days to any other FVIII products (prevention or treatment of bleeds).

4. No detectable inhibitors to FVIII (≥0.6 BU/mL) (as assessed by a special laboratory at the time of screening).

5. If HIV-1 seropositive, viral load <400,000 copies/mL and CD4+ lymphocyte count ≥200/µL.

Eligibility criteria for subjects undergoing surgery:

1. Documented history of at least 150 exposure days to any FVIII concentrates (preventative or on-demand regimen).

2. Subjects requiring major or minor surgical procedures.

Eligibility criteria for subjects participating in PK sub-trial in subjects with BMI ≥30 kg/m^2:

1. Informed consent obtained prior to any trial-related activities.

2. BMI ≥ 30 kg/m^2

3. Subjects aged 12 or above.

Exclusion criteria for the main trial:

1. Previous participation in the current trial (defined as withdrawal) or withdrawn subjects from NN7008-3522, NN7008-3543, NN7008-3545, NN7008-3600, NN7008-3893 or NN7008-4015 after administration of trial product, unless the previous trial protocol declares that the subject is allowed to be transferred to NN7008-3568 trial.

Main exclusion criteria for new subjects starting in the 6-month on-demand sub-trial:

1. Any history of FVIII inhibitors.

2. Known or suspected allergy to trial product (turoctocog alfa) or related products.

3. Subjects undergoing or planning to undergo immune modulating medication.

4. Known pseudo-tumours.

5. Platelet count <50,000 platelets/µL based on medical records and/or based on local laboratory values at trial entry.

Main withdrawal of patients from therapy and assessment

A patient had to be withdrawn if one of the following withdrawal criteria applied:

1. Haemostasis not achievable with turoctocog alfa.

2. Allergy to trial product.

3. Detectable inhibitors to FVIII (≥0.6 BU).

In summary, 16 criteria for patient withdrawal have been defined in the study protocol.

Treatments

Patients received either a preventive regimen with scheduled preventive turoctocog alfa infusions (20−50 IU/kg BW once every second day or 20−60 IU/kg BW three times weekly [standard prophylaxis dosing regimen]; 40−60 IU/kg BW twice weekly or once every third day [less frequent dosing regimen]) with additional treatment for bleeds or on-demand treatment of bleeds as they occurred and occasionally as preventive treatment (for example, before physical activity). Dose levels up to 200 IU/kg per day could be used depending on the severity and location of the bleed. Dose levels for treatment of bleeds were 20-50 IU/kg BW. In total up to 150 IU/kg BW per day could be used to treat severe bleeds. Doses totalling up to 150 IU/kg BW per day could be used at the discretion of the Investigator to treat subjects during elective surgery. Bolus and continuous infusion with turoctocog alfa could be chosen during surgery. If a haemostatic response could not be achieved after 48 hours using maximal doses of turoctocog alfa when treating bleeds, another FVIII product could be selected at the discretion of the investigator, and the patient was withdrawn from the trial. No placebo and no comparators were included in the trial.

In the PK sub-trial, patients were administered a single dose of 50 IU/kg turoctocog alfa followed by blood sampling for PK evaluation over 3 days with an optional sampling on the 4th day.

Outcomes/endpoints

Primary endpoints:

- Frequency of development of FVIII inhibitors (≥0.6 BU/mL)
- Frequency of AE, SAE and MESI (Medical Event of Special Interest) reported.

Secondary endpoints:

The secondary endpoints for preventative regimen are:

- Average number of bleeds per month reported during the prevention period
- Haemostatic response to N8 (none, moderate, good or excellent) in treatment of bleeds.

The secondary endpoint for on-demand regimen is:

- Haemostatic response to N8 (none, moderate, good or excellent) in treatment of bleeds

Endpoints for the sub-trial:

Primary endpoints for the sub-trial

- Assessment of haemostatic effect of N8 during surgery
- Amount of blood products transfused
- Loss of blood (actual)
- Assessment of the actual consumption of N8 (IU/kg BW)
    - Surgery period
    - Recovery period

Pharmacokinetic endpoints for the sub-trial

- Incremental recovery of FVIII (defined as the FVIII level 30 min. after infusion and reported as [IU/mL]/[IU/kg])

- AUC
- Half-life ($t_{½}$)
- Clearance (CL)

Secondary endpoints for the Sub-Trial

- Frequency of AE, SAE and MESI reported during the surgery and recovery period

Statistical Methods

Determination of sample size:

The sample size was based on the number of patients who completed the studies NN7008-3543, NN7008-3545, NN7008-3600, NN7008-3893 and NN7008-4015 and the number of patients that would participate in the on demand sub-trial. It was estimated that a total of up to 214 patients would participate in the trial.

Definition of analysis sets:

The FAS included all dosed patients. All main descriptions and analyses of safety and efficacy data were based on the full analysis set (FAS). FVIII inhibitor development during the trial was summarised and listed by age group and by type of regimen (i.e. for preventive and on-demand regimen, respectively).

Efficacy:

All efficacy endpoints were to be reported using treatment requiring bleeds only. As a sensitivity analysis, the annualised bleeding rate was to be calculated for both treatment-requiring bleeds and non-treatment requiring bleeds. The haemostatic response to turoctocog alfa evaluated according to a predefined four point scale (none, moderate, good or excellent) was to be presented using counts and percentages of all treatment requiring bleeds. The haemostatic effect of turoctocog alfa was also to be presented using a success/failure rate. Bleeds evaluated as excellent and good were to be counted as success and bleeds evaluated as moderate and none were to be counted as failure. The success/failure rate was to be repeated counting bleeds with missing evaluation as failure.

The number of infusions required to treat a bleed (from start to stop of the bleed) were to be presented using counts and percentages of all treatment-requiring bleeds. Furthermore, the number of infusions of turoctocog alfa per treatment requiring bleed was to be summarised and listed.

Classification of re-bleed was to be performed at the time of the statistical analysis, according to the following criteria: A re-bleed is defined as a new bleed (worsening of bleeding site conditions e.g. swelling, pain) within 72 hours after stopping of a previous bleed at the same or a subset of the same anatomical locations. All summary tables regarding the haemostatic response and the number of infusions required to treat a bleed were to be presented by age group and by type of regimen.

The annualised bleeding rate in total and by cause of bleed, excluding bleeds occurring more than 72 hours after last turoctocog alfa dose, was to be presented with a 95% confidence interval for subject on preventative regimen.

The number of hours since last turoctocog alfa dose when a treatment-requiring bleed occurs were to be summarised and listed for subjects on preventive regimen.

The consumption of turoctocog alfa used for prevention and the consumption used for treatment of bleed was to be summarised and listed for subjects on preventive regimen.

The consumption of turoctocog alfa used for treatment of bleed was to be summarised and listed for subjects in the on demand regimen.

Safety:

The primary endpoint was the frequency of development of FVIII inhibitors (≥0.6 BU). FVIII inhibitor development during the trial was summarised and listed by age group and by type of regimen. (i.e. for preventive and on-demand regimen, respectively). The secondary safety endpoints: AEs and SAEs reported during the trial were summarised in total, in relation to the preventive regimen and in relation to the on demand regimen.

The primary endpoint for the surgery part of the trial was haemostatic effect of turoctocog alfa assessed by evaluation according to a predefined four point scale: none, moderate, good or excellent. Secondary efficacy endpoints for the surgery part of the trial were assessment of the actual consumption of turoctocog alfa (IU/kg) in the time period day 1 to day 7 and in the time period day 8 to return to pre-surgery regimen; comparison of actual and anticipated blood loss; haemoglobin level prior to surgery, during, and after surgery (pre-operative, intra-operative and post-operative) and blood product transfusion. Evaluation of efficacy during surgery was based on descriptive statistics.

Results

Recruitment/ Number analysed

A total of 214 patients were enrolled and 213 of these were dosed with turoctocog alfa in the trial. One patient withdrew before dosing and was therefore excluded from the full analysis set (n=213). A total of 82 patients were withdrawn from the trial: 2 patients due to AEs, 3 due to non-compliance with the protocol, 13 due to meeting withdrawal criteria, and 64 due to reasons categorised as 'other'. 43 of the latter withdrew from the trial to join a Novo Nordisk pathfinder trial.

The majority of enrolled patients (n = 207) was treated prophylactically in the main trial and a total of 9 patients were on an on-demand regimen (sub-trial FAS n=14) with few patients switching between both regimen. Overall, 130 patients completed the main trial. A total of 17 patients participated in the surgery sub-trial. 18 major surgeries were performed in 14 patients and 3 minor surgeries in 3 patients during the trial. 6 patients participated in the PK sub-trial.

Baseline data

The study population consisted of male patients with severe haemophilia A (FVIII activity ≤1%) and was divided into 4 age groups: small children (0 to <6 years, n=27), older children (6 to <12 years, n=28), adolescents (12 to <18 years, n=23) and adults (≥18 years, n=135). The majority of the patients were White (83.1%) and the second largest group was the Asian population (11.3%). Patients participating in the PK sub-trial had a mean BMI of 33.35 kg/m^2.

Efficacy results

Annualised bleeding rate:

- The overall estimated annualised bleeding rate among patients following a preventive regimen was 2.44 bleeds/patient/year (95% CI: 2.06−2.89 bleeds/patient/year) during a total of 730.8 years, with 1.86 bleeds/patient/year in small children, 2.88 bleeds/patient/year in older children, 1.96 bleeds/patient/year in adolescents and 2.59 bleeds/patient/year in adults.

- The overall estimated annualised bleeding rate among patients following a preventive less frequent dosing regimen was 2.01 bleeds/patient/year (95% CI: 1.21−3.33 bleeds/patient/year) during a total of 16.9 years, with no bleeds in small children (n=2), 2.62 bleeds/patient/year in older children, 2.69 bleeds/patient/year in adolescents and 1.32 bleeds/patient/year in adults.
- The overall estimated annualised bleeding rate among patients following on-demand regimen was 24.02 bleeds/patient/year (95% CI: 16.90−34.15 bleeds/patient/year) during a total of 16.3 years, with 18.49 bleeds/patient/year in the on-demand regimen of the main trial and 32.36 bleeds/patient/year in the on-demand sub trial. The annualised bleeding rate reported in adults only in both the on-demand regimen of the main trial and on demand sub-trial was 24.96 bleeds/patient/year.

Median annualised bleeding rate:

- The overall median annualised bleeding rate among patients following a preventive regimen was 1.37 bleeds/year (IQR: 2.96).
- The overall median annualised bleeding rate among patients following a preventive less frequent dosing regimen was 0.00 bleeds/year (IQR: 3.63).
- The overall median annualised bleeding rate among patients following on-demand regimen was 30.44 bleeds/year (IQR: 28.10).

Success rate:

- During the preventive regimen, the success rate for treatment of bleeds in the FAS was 89.8% when bleeds with missing evaluation of haemostatic response were counted as failure and 90.2% when missing evaluations were excluded.
- During the preventive less frequent dosing regimen, the success rate for treatment of bleeds in the FAS was 94.1%; there were no bleeds with missing evaluation of haemostatic response in this regimen.
- During the on-demand treatment, the success rate for the treatment of bleeds in the FAS was 96.7%; there were no bleeds with missing evaluation of haemostatic response in this regimen.

Number of injections needed to stop bleeds:

- Of the 1,782 reported bleeds during the preventive regimen, 1,297 (72.8%) were stopped with 1 injection of turoctocog alfa, 275 (15.4%) were stopped with 2 injections and 101 (5.7%) were stopped with 3 injections.
- During the preventive less frequent dosing regimen, of the 34 reported bleeds, 26 (76.5%) were stopped with 1 injection of turoctocog alfa, 6 (17.6%) were stopped with 2 injections and 2 (5.9%) were stopped with 3 injections.
- Of the 391 reported bleeds during the on-demand regimen, 310 (79.3%) were stopped with 1 injection of turoctocog alfa, 61 (15.6%) were stopped with 2 injections and 15 (3.8%) were stopped with 3 injections and 5 (1.3%) were stopped with 4 injections.

Efficacy in surgery:

- The haemostatic response for the 18 major and 3 minor surgeries was rated as "excellent" or "good" both during and after surgery.

Consumption:

- In the preventive regimen, the mean dose was 32.5 IU/kg BW and the mean consumption per patient per year for prevention was 5,094 IU/kg BW/year/patient. The mean consumption used for treatment of a bleed from start to stop of a bleed was 62.1 IU/kg BW/bleeding episode for patients during the preventive regimen.
- The mean dose used during the preventive less frequent dosing regimen was 48.2 IU/kg BW and the mean consumption per patient per year for prevention was 5,432 IU/kg BW/year/patient. The mean consumption used for treatment of a bleed from start to stop of a bleed was 53.6 IU/kg BW/bleeding episode for patients during the preventive regimen.
- The mean dose used during the on-demand regimen was 36.2 IU/kg BW and the mean consumption used for treatment of a bleed from start to stop of a bleed was 43.9 IU/kg BW/bleeding episode.
- In regard to total consumption of turoctocog alfa and annualised bleeding rate, patients on the preventive regimen consumed a mean total of 5284 IU/kg BW/year/patient, which was three-fold higher than the mean total consumption of turoctog alfa during the on-demand regimen (1505 IU/kg BW/year/patient). Increased consumption in the preventive regimen was associated with a 90% reduction in annualised bleeding rate compared to that reported during the on-demand regimen (2.44 vs 24.02 bleeds/patient/year, respectively).
- In surgery, consumption differed largely and total consumption ranged between 225 IU/kg (i.e. a case of major surgery of gall stones) and 6711 IU/kg (i.e. major surgery in case of arthropathia haemophilia requiring 140 days under surgery regimen) of turoctocog alfa.

Safety results

- No FVIII inhibitors were detected.
- Overall, a total of 1278 AEs were reported for 184 (86.4%) patients exposed to turoctocog alfa), including patients undergoing surgery, corresponding to an AE rate of 1.7 (1278/756.7) events per patient year of exposure.
- The most frequently reported AEs during the preventive regimen were headache (0.12 events per patient year of exposure), nasopharyngitis (0.09 events per patient year of exposure), upper respiratory tract infection (0.07 events per patient year of exposure) and pharyngitis (0.07 events per patient year of exposure).
- 12 events in 8 of 213 patients were judged by the investigator to be possibly or probably related to turoctocog alfa; 11 out of 12 events were non-serious and of mild or moderate severity. One event of acute myocardial infarction in a 41 year old patient on-demand regimen of the main trial was considered serious and severe.
- A total of 49 SAEs (including 2 deaths) were reported in 41 patients. 46 SAEs were reported during the preventive regimen, 1 during on-demand regimen and 2 during surgery. All SAEs except for 1 were judged by the investigator as unlikely related to turoctocog alfa treatment.
- No events of hypersensitivity were assessed as related to turoctocog alfa.
- Laboratory parameter assessments and other safety-related examinations did not indicate clinically significant changes as a result of turoctocog alfa administration.

Pharmacokinetic results

- The mean incremental recovery (chromogenic assay) was 0.035 (IU/mL)/(U/kg) and the mean AUC_{0-t} (chromogenic assay) was 29.98 IUxh/mL; both parameters were higher than those expected in persons with normal weight.
- The mean $t_{½}$ (chromogenic assay) was 12.40 h and the mean CL (chromogenic assay) was 1.94 ml/h/kg. This result was expected in patients with higher body mass who have less plasma per kg body weight compared to persons with normal body composition.

1.3.3. Discussion on clinical aspects

In accordance with Article 46 of Regulation (EC) No. 1901/2006, the MAH submitted the final report of a phase 3b trial assessing safety and efficacy of turoctocog alfa in prevention and on-demand treatment of bleeding episodes in subjects with haemophilia A. The clinical study also included a surgery and PK sub-trial. Of the 213 treated subjects, 78 were pediatric patients including 55 patients below the age of 12. All patients participating in the PK sub-trial were adult and in the surgery sub-trial, 3 from 17 patients were children (6-12 years of age) and 1 patient was adolescent. In general, the treatment with turoctocog alfa was well tolerated in all parts of the trial exhibiting a safety profile which was in line with expectations. No FVIII inhibitors or hypersensitivity events occurred in this trial. From 8 patients who experienced adverse events judged as being possibly or probably related, 7 patients were adult and 1 patient was adolescent (14 years of age). The latter was diagnosed with a mild lichenoid keratosis/dermatitis which was judged as probably related and did not recover. No Lupus anticoagulant or relevant abnormalities were detected in hematologic and biochemistry safety analyses of this patient. FVIII recovery was regular and the patient was negative for FVIII inhibitor, HIV, hepatitis B and C. No specific clustering of this and the remaining possibly or probably treatment related SAE can be detected. Overall, no safety issues can be identified from this clinical trial.

Efficacy of turoctocog alfa was demonstrated during both preventive treatment regimens as well as for on-demand treatment. Efficacy was also shown when used in major and minor surgeries (i.e. good or excellent haemostatic response during or after surgery). In accordance to the current guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products, age-stratified data on FVIII consumption for prophylaxis, on-demand therapy and during surgery are provided. In general, consumption in both preventive treatment regimens was higher in younger and older children when compared to adults. Regarding consumption and ABR, data for the standard (i.e. consumption of 5,094 IU/kg BW/year/patient, ABR 2.44 bleeds/patient/year) and the less frequent (i.e. consumption of 5,432 IU/kg BW/year/patient, ABR 2.01 bleeds/patient/year) prophylaxis dosing regimen were largely the same.

Overall, safety and efficacy data of pediatric patients provided by this study report are sufficiently covered by the current SmPC. It can be agreed that no regulatory consequences have been identified.

Rapporteur's overall conclusion and recommendation

In summary, the data reported from study no. NN7008-3568 confirm safety and efficacy of turoctocog alfa used in prophylaxis and on-demand treatment regimen as well as during surgery procedures in pediatric patients. The current benefit-risk profile remains unchanged and data from this study are adequately reflected in the current SmPC. No regulatory action required. No additional clarification requested.

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☒ **Fulfilled**

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

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: Active substance:

Study title	Study number	Date of completion	Date of submission of final study report
A multi-centre, multinational, open-label, safety, efficacy, singlearm trial in patients with severe haemophilia A investigating turoctocog alfa when used for prevention and treatment of bleeds. The trial included a subtrial 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	29 September 2011	15 October 2012
A multi-centre, open-label, noncontrolled safety and efficacy trial of turoctocog alfa in previously treated paediatric patients withhaemophilia A.	NN7008-3545	21 November 2011	15 October 2012