

Final Statistical Review and Evaluation - Novoeight

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Statistical Review and Evaluation

BLA (FINAL REVIEW)

BLA Supplement Number: STN 125466

Product Name: turoctocog alfa

Indication(s):

Control and prevention of bleeding episodes in adults, adolescents and children with hemophilia A; perioperative management of patients with hemophilia A; routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults, adolescents and children

Applicant: Novo Nordisk

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1. EXECUTIVE SUMMARY

The sponsor submitted a biologic licensure application for NovoEight, Antihemophilic Factor (Recombinant), plasma/Albumin-Free for the following indications:

- Control and prevention of bleeding episodes in adults, adolescents and children with hemophilia A;
- Perioperative management of patients with hemophilia A;
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults, adolescents and children.

The primary objective was the evaluation of the safety of turoctocog alfa. For the phase 3 pediatric study, over a minimum of 50 exposure days per subject, no Factor VIII (FVIII) inhibitors were detected and the one-sided 97.5% upper confidence limit for the inhibitor incidence rate was 6.06%. For the phase 3 study in adolescents and adults, over a minimum of 50 exposure days per subject, no FVIII inhibitors were detected and the one-sided 97.5% upper confidence limit for the inhibitor incidence rate was 2.46%. For both trials, the primary evaluations of safety met their respective pre-specified success criteria.

The protocol did not specify the success criteria to claim the efficacy of turoctocog alfa for prevention and treatment of bleeds. No formal statistical testing was performed to evaluate the efficacy of the study, but instead summary statistics were provided. This reviewer defers to the clinical reviewer to decide the efficacy success criteria.

2. INTRODUCTION

2.1 Overview

A placebo-controlled trial in subjects with severe haemophilia A would be unethical because of the risk of serious bleeding complications. Therefore, Novo Nordisk studied the safety and efficacy of turoctocog alfa in uncontrolled, multicenter and open-label phase 3 trials. The primary objective of these trials was to evaluate the safety of turoctocog alfa. The overall evaluation of safety was based on information from five

completed clinical trials (Trials 3522, 3893, 3600, 3543, and 3545) as well as safety information from Trial 3568 (see Table 1).

Table 1. Overview of Clinical Trials (Source: clinical overview.pdf from 125466/0.0 module II)

Trial ID	Phase	Doses	Number of dosed patients	Trial status	Trial description
Trial 3522	Phase 1	50 IU/kg (single dose) Advate®: 50 IU/kg (single dose)	23 adolescent or adult patients with severe haemophilia A	Completed	<i>First human dose trial</i> A multicentre, multinational, open-label, first human dose, pharmacokinetic, safety, single-dose trial using a sequential design in patients with haemophilia A.
Trial 3893	Phase 1	50 IU/kg (single dose)a	4 adult patients with severe haemophilia A	Completed	<i>Pharmacokinetic trial (two lots)</i> A multicentre, open-label, trial investigating the pharmacokinetics of a single dose of turoctocog alfa in patients with haemophilia A.
Trial 3600	Phase 1	50 IU/kg (single dose)a	7 adult patients with severe haemophilia A <i>Pharmacokinetics:</i> 6 patients	Completed	<i>Pharmacokinetics in Japanese patients</i> A multicentre, open-label, single-dose trial investigating the pharmacokinetics of turoctocog alfa in Japanese patients with haemophilia A.
Trial 3543	Phase 3	<i>Prevention:</i> 20–40 IU/kg every second day or 20–50 IU/kg three times weekly. <i>Treatment of bleeds and surgery:</i> At the investigator's discretion. <i>Pharmacokinetics:</i>	<i>Total (including sub-trial):</i> 150 adolescent or adult patients with severe haemophilia A. <i>Surgery sub-trial:</i> 9 patients <i>Pharmacokinetics:</i> 22 patients (same	Completed	<i>Pivotal trial</i> A multicentre, multinational, open-label, safety, efficacy, single-arm trial in patients with severe haemophilia A investigating turoctocog alfa when used for prevention and treatment of

Trial ID	Phase	Doses	Number of dosed patients	Trial status	Trial description
		50 IU/kg (single dose) preceded by preventive dosing for 3–6 months (wash-out period of ≥ 4 days prior to the pharmacokinetic session).	patients as in Trial 3522)		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. The pharmacokinetics of turoctocog alfa was assessed following 3–6 months of preventive dosing in patients who had completed Trial 3522.
Trial 3545	Phase 3	<i>Pharmacokinetics:</i> 50 IU/kg (single dose). Patients' previous product: 50 IU/kg (single dose) <i>Prevention:</i> 25–50 IU/kg every second day or 25–60 IU/kg three times weekly. <i>Treatment of bleeds and surgery:</i> At the investigator's discretion.	<i>Total:</i> 63 paediatric patients (below 12 years of age) with severe haemophilia A. <i>Pharmacokinetics:</i> 28 patients	Completed	<i>Paediatric trial</i> A multicentre, open-label, non- controlled safety, efficacy and pharmacokinetic trial of turoctocog alfa in paediatric patients with haemophilia A.
Trial 3568	Phase 3	<i>Prevention:</i> 20–50 IU/kg every second day or 20–60 IU/kg three times weekly. <i>Treatment of bleeds/on- demand and surgery:</i> At the investigator's	<i>Total (including sub-trial):</i> 187 paediatric, adolescent or adult patients with severe haemophilia Ab <i>Surgery sub-trial:</i>	Ongoing	<i>Extension trial</i> A multicentre, multinational, open-label, non-randomised, single-arm, safety and efficacy extension trial in patients with haemophilia A investigating

Trial ID	Phase	Doses	Number of dosed patients	Trial status	Trial description
		discretion.	2 patients		turoctocog alfa when used in a preventative or on-demand treatment regimen. The trial includes a sub-trial designed to evaluate safety and efficacy of turoctocog alfa during surgery.

The efficacy of turoctocog alfa in prevention of bleeds, treatment of bleeds and during surgery, was investigated in three multicenter, open-label, uncontrolled phase 3 trials (Trials 3543, 3545, and 3568) in previously treated subjects with severe hemophilia A. Since appropriate pharmacokinetic data are regarded as the most important surrogate endpoint for efficacy of a new FVIII product, no comparators were used in the assessment of clinical efficacy endpoints. Therefore the evaluation of efficacy was conducted by summary statistics and no formal statistical testing was performed. This review only focuses on the primary safety evaluation. Since Trials 3522, 3893 and 3600 are pharmacokinetic trials, only Trials 3543, 3545 and 3568 are included in the review memo.

2.2 Data Sources

All data sources are included in the sponsor's eCTD submission located in the FDA/CBER Electronic Data Room (EDR).

Reviewer Comment: Novo Nordisk submitted an amendment on 23 April 2013 providing additional information on datasets and programs for the review of the study results. The amendment states that the inhibitor test result itself is stored in the value AVAL. This reviewer has discussed with the clinical reviewer that "AVAL" is a typographical error and that the variable AVALC stored the value for the inhibitor result.

3. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

3.1 Trial 3543

3.1.1 Study Design

Study Design and Objectives:

The trial is a multicenter (15 sites), multi-national, open-label, safety, efficacy, single-arm trial in subjects with hemophilia A (FVIII deficiency). The subjects were recruited at 48 sites in 15 countries. The trial included three parts: Part A included subjects who completed the pharmacokinetic trial (Trial 3522); Part B included subjects who participated in the trial and who did not participate in the pharmacokinetic trial; Part C included subjects from Part A or Part B undergoing surgical procedures.

Originally, the primary objective was efficacy. After the trial was initiated on 7 April 2009, the primary objective was changed to safety with Amendment 14 (dated 15 October 2009). The primary objective for Part A, Part B, and Part C is to assess the incidence rate of FVIII inhibitors (≥ 0.6 BU).

Secondary objectives of Part A and Part B include:

- To evaluate the clinical efficacy of turoctocog alfa in bleeding prevention in subjects with hemophilia A
- To evaluate the clinical efficacy of turoctocog alfa when treating bleeds in subjects with hemophilia A
- To evaluate the safety of turoctocog alfa when used for prevention of bleeds and treatment of mild/moderate and severe bleeds in subjects with hemophilia A
- To assess changes in patient-reported outcomes (PROs) from screening to the end of the trial

Secondary objectives of only Part A include:

- To describe and compare the pharmacokinetic profile of turoctocog alfa in subjects with hemophilia A

Secondary objectives of Part C include:

- To evaluate the efficacy of turoctocog alfa during surgical procedures in subjects with hemophilia A
- To evaluate the haemostatic response to turoctocog alfa in the post-surgery period for subjects with hemophilia A
- To evaluate the safety of turoctocog alfa when used for prevention and treatment of bleeding during surgical procedures and in the surgery period in subjects with hemophilia A
- To assess changes in PROs from pre-surgery to last day of the surgical recovery period

Endpoints:

(1) Primary safety endpoint: the incidence rate of FVIII inhibitors (≥ 0.6 BU)

(2) Secondary safety endpoints:

Parts A and B:

Frequency of adverse events (AEs) and serious adverse events (SAEs) reported during the trial period; Vital signs (blood pressure, pulse, temperature, and respiratory rate)

(3) Secondary efficacy endpoints:

Parts A and B:

Total consumption of turoctocog alfa per subject (prevention and treatment of bleeds) per month; Actual consumption of turoctocog alfa (IU/kg /month) for prevention; Average number of bleeds per month; Haemostatic effect of turoctocog alfa evaluated according to a predefined four-point scale (none, moderate, good or excellent); Number of infusions of turoctocog alfa required per bleeding episode; Time to control of bleeding after the first dose of turoctocog alfa used for treatment of bleeds; Actual consumption

of turoctocog alfa (IU/kg /bleed)

Part C:

Haemostatic effect of turoctocog alfa assessed by evaluation according to a predefined four point scale (none, moderate, good or excellent); 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 preventative treatment; Comparison of actual and anticipated blood loss; Hemoglobin level prior to surgery, during, and after surgery (pre-operative, intra-operative, and post-operative); Blood product transfusion

Sample Size:

The planned number of subjects to be started on turoctocog alfa was 140.

Randomization Scheme:

The trial was not randomized.

Blinding:

This was an open-label trial.

Population Proposed and Analyzed in the Protocols and BLA:

Subjects who were actually dosed with turoctocog alfa were included in the full analysis set (FAS) on which all the efficacy analyses are based. All evaluations of safety were based on the safety analysis set (all dosed subjects) and thus is identical to the FAS.

Interim Analysis:

An interim analysis took place after the first 20 subjects had 50 exposure days each. The purpose of the interim analysis was to ensure adequate safety and efficacy with turoctocog alfa in order to initiate the pediatric trial (Trial 3545). The results of the interim analysis are not presented. The interim analysis discovered a quality issue with the patient-reported diary data. The analyses made on bleeds were repeated without the data from before the interim analysis. Detailed information on the interim analysis can also be found in the Protocol Amendments and Deviations section of this review memo.

Protocol Amendments and Deviations:

There are 22 substantial amendments to the protocol included in the report. This review only focuses on the ones related to the study design and statistical analysis.

(1) Amendment No. 9 and Amendment No. 14 made some major changes on the primary objectives, endpoints, the corresponding statistical hypothesis and testing method. The revised protocol was reviewed by the Division of Biostatistics (see detailed IND statistical review memo dated 19 November 2009)

(2) Protocol deviation (changes after database lock): Early in the trial, a quality issue with the patient-reported diary data was discovered at the trial site in Israel, which resulted in an audit at the site. Consequently, the analyses made on bleeds were repeated without the subjects from Israel. In addition, an interim analysis conducted 16 February 2010 discovered that some subjects had misunderstood the category 'none' on the four-point scale for haemostatic response. The subjects mistakenly thought that this category should be checked if the haemostatic response was not evaluated by the investigator instead of using this category for the intended purpose of rating the treatment as not working. After this was discovered, diary training was prepared and distributed to the sites with a clear explanation of the category 'none' in order to avoid this mistake. Therefore, the analyses made on bleeds were repeated without the data

from before the interim analysis. Since the analyses were conducted without the data from before the interim analysis, the impact of this deviation is minor.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 172 subjects were screened for this trial and 150 of these subjects were dosed with turoctocog alfa. A total of four subjects (three adults and one adolescent) withdrew from the trial for the following reasons: AEs (subject number -(b)(6)-); treatment with a FVIII containing product other than turoctocog alfa (subject number -(b)(6)-); lost to follow-up (subject number -(b)(6)-) and positive inhibitor test of 1 BU at another medical facility in 2008, but the test result was not available to the investigational site at the time of enrolment (subject number -(b)(6)-). When the inhibitor test result became available to the investigational site, the subject was withdrawn. For these subjects, data was included up to the time of withdrawal.

Of the 150 subjects who were dosed, 22 subjects had previously participated in the first human dose trial (Trial 3522) with turoctocog alfa and were thus included in Part A of the trial. The remaining 128 dosed subjects were included in Part B. In addition, nine subjects who had participated in either Part A or B participated in the surgery sub-trial (Part C).

Of the 150 subjects dosed with turoctocog alfa, 100% were males with severe hemophilia (FVIII activity $\leq 1\%$), a mean age of 28 years old (ranging from 12 to 60 years old), a mean weight of 73.2 kg (ranging from 32.7 to 120.0 kg) and a mean BMI of 24.1 kg/m² (ranging from 13.8 to 40.4 kg/m²). The majority of the subjects were White (80.7%) and the second-largest group was Asian (13.3%). Nineteen percent (19%) of the subjects were from the US, 13% were from Serbia and 11% were from Brazil, while the remaining 57% of the subjects were distributed between 12 other countries. Among the 24 adolescents, the mean age was 14 years old (ranging from 12 to 17 years old), the mean weight was 52.6 kg (ranging from 32.7 to 95.0 kg) and the mean BMI was 19.3 kg/m² (ranging from 13.8 to 32.5 kg/m²).

3.1.3 Statistical Methods

Primary safety endpoint:

The incidence rate was calculated and a one-sided 97.5% upper confidence limit was provided based on an exact calculation for a binomial distribution. For the calculation of the rate, the numerator included all subjects with inhibitors while the denominator included all subjects with a minimum of 50 exposure days plus any subjects with less than 50 exposure days but with inhibitors. Adequate safety with regard to inhibitors was concluded if the upper one-sided 97.5% confidence limit was below 6.8%.

Secondary efficacy endpoints:

Parts A and B:

(1) Consumption of turoctocog alfa

Total actual consumption of turoctocog alfa (IU/kg BW) per subject was calculated for prevention (per month and per year) and for treatment of bleeds. Actual consumption of turoctocog alfa (IU/kg BW/bleed) per subject per bleed for treatment of bleeds was

calculated as the consumption of turoctocog alfa used from the start of the bleed to the stop of the bleed. The total actual consumption of turoctocog alfa per subject (prevention and treatment of bleeds) was calculated as the sum of the entire consumption of turoctocog alfa.

(2) Prevention of bleeds

The annualized bleeding rate was estimated in total and by cause of bleed (spontaneous, traumatic or other) based on a Poisson model allowing for overdispersion. No formal statistical testing was performed. The estimated mean bleeding rates are presented for all subjects and separately for adolescents and adults. The annualized bleeding rate was also estimated by country and by compliance group. Definition of good compliance: If both criteria below were fulfilled, a subject was considered in good compliance with the preventive regimen.

- The preventive doses of turoctocog alfa were within the dose range (defined as 2560 IU/kg for the three times weekly dosing regimen and as 2550 IU/kg for every second day dosing regimen) for at least 80% of the preventive doses.
- No less than three preventive doses/week were taken for at least 80% of the weeks. Definition of less compliance: If one or both criteria below were fulfilled, a subject was considered in less compliance with the preventive regimen.
- More than 20% of the preventive doses were outside the dose range (defined as 2560 IU/kg for the three times weekly dosing regimen and as 2550 IU/kg for every second day dosing regimen).
- Less than three (or greater than four for every second day dosing regimen) preventive doses/week were taken for more than 20% of the weeks.

(3) Treatment of bleeds

Haemostatic effect of turoctocog alfa used for treatment of acute bleeds was evaluated according to a predefined four-point scale (none, moderate, good or excellent).

Haemostatic effect was presented using counts and percentages of bleeding episodes. If the haemostatic response was rated as excellent or good, the treatment of the bleed was counted as a success. If the haemostatic response was rated as moderate or none, the treatment was counted as a failure. As a conservative approach, the missing ratings were included as treatment failures. Furthermore, the haemostatic effect of turoctocog alfa was summarized by cause of bleed (spontaneous, traumatic or other), site of the bleed (central nervous system, joint, gastrointestinal, subcutaneous, muscular or other), classification of the bleed (mild/moderate or severe), time of the bleed (the day was divided into six time intervals, each of four hours), and compliance (good compliance or less compliance), respectively.

Part C:

Evaluation of data was based on descriptive statistics.

3.1.4 Results and Conclusions

The following summarizes the analysis results for Trial 3543 (source: report-body.pdf in submission section 5.3.5.2.3):

Primary safety endpoint:

- No FVIII inhibitors were detected. The one-sided 97.5% upper confidence limit for the inhibitor incidence rate of zero was 2.46%, thus the primary evaluation of adequate safety (upper confidence limit below 6.8%) criteria has been met.
- Since there was no FVIII inhibitors detected, no subgroup analysis by gender, age or race/ethnicity was conducted.

Secondary safety endpoints:

- A total of 225 AEs were reported in 100 (67%) subjects and every subject has at least one AE reported. The most commonly reported AEs were related to dosing (incorrect dose administered was reported for 15 subjects (10%) , wrong technique in drug usage process was reported for two subjects (1.3%) and an overdose was reported for one subject(0.7%)), headache (reported for 15 subjects (10%)) and nasopharyngitis (reported for 12 subjects (8%)).
- Of a total of 222 adverse events reported in 99 (66%) subjects during preventive treatment (part A + B), 17 events were evaluated by the investigator to be possibly or probably related to trial product. These events were all of mild or moderate severity.
- Nine (9) subjects underwent surgery (part C). Three (3) mild or moderate adverse events evaluated as unlikely related to trial product by the investigators were recorded in 3 subjects during surgery.
- Of the 225 AEs, 32 AEs were reported from 12 subjects with age less than or equal to 16 years, 16 AEs were reported from 10 subjects with age between 16 and 18years, 108 AEs were reported from 49 subjects with age between 18 and 30 years, and 69 AEs were reported from 29 subjects older than 30 years.
- No thromboembolic events or allergic type hypersensitivity reactions occurred during the trial.

Secondary efficacy endpoints:

- Of the 499 reported bleeds, 89.4% were stopped with one or two infusions of turoctocog alfa.
- The total consumption per month per subject for prevention and treatment of bleeds was 338 IU/kg subject/month (ranged from 222 to 747 IU/kg/subject/month), and was higher for subjects in good compliance than for subjects who were less compliant.
- The majority of the bleeds (66.5%) were spontaneous and the majority of the bleeds (90%) were classified as mild/moderate. The estimated annualized bleeding rate (spontaneous and traumatic) was 6.50 bleeds/subject/year. The estimated mean bleeding rate for spontaneous bleeds was 4.32 bleeds/subject/year (3.15 bleeds/subject/year for adolescents and 4.55 bleeds/subject/year for adults). The rate of traumatic bleeds was 2.07 bleeds/subject/year for adolescents and 1.53 bleeds/subject/year for adults. The annualized bleeding rate varied considerably among countries and was lower for subjects in good compliance than for subjects who were less compliant.
- The success rate for treatment of bleeds was 84.5% (excluding bleeds for which there was no outcome reported). A more conservative approach (considering bleeds for which there was no reported outcome as treatment failures) gave a success rate of 80.8% for treatment of bleeds.
- Homeostasis was successful in all 9 (8 major and 1 minor) surgeries.

3.2 Trial 3545

3.2.1 Study Design

Study Design and Objectives:

The trial is a multicenter (11 sites), open-label, non-controlled safety and efficacy trial of turoctocog alfa in previously treated subjects <12 years of age with hemophilia A. The primary objective of the trial is to evaluate safety. The secondary objectives are to evaluate the pharmacokinetics; to evaluate efficacy and to assess and compare PROs from baseline to the end of the trial.

Endpoints:

(1) Primary safety endpoint: The incidence rate of FVIII inhibitors (≥ 0.6 BU).

(2) Secondary safety endpoints: Frequency of AEs and SAEs.

(3) Secondary efficacy endpoints:

Bleeding prevention:

Total consumption of turoctocog alfa per subject (prevention and treatment of bleeds) per month and annualized value; Actual consumption of turoctocog alfa (IU/kg /month) for bleeding prevention; Average number of bleeds per year.

Treatment of bleeds:

Haemostatic effect of turoctocog alfa on treatment of bleeds assessed on a predefined four-point scale: none, moderate, good or excellent; Number of infusions of turoctocog alfa per bleed; Actual consumption of turoctocog alfa (IU/kg /bleed) for treatment of bleeds.

Sample Size:

The planned number of subjects to be started on trial product was 60.

Randomization Scheme:

The trial was not randomized.

Blinding:

This was an open-label trial.

Analysis Populations:

All subjects who were dosed with turoctocog alfa were to be included in the FAS on which all the efficacy analyses, including analyses of patient-reported outcomes, are based. The safety analysis set was identical to the FAS.

Protocol Amendments and Deviations:

There are five substantial protocol amendments and none are related to the study design and statistical analysis.

Two protocol deviations were reported in the submission. Since the standard way of reporting bleeding rates is annualized, the estimated annualized bleeding rate was reported rather than the monthly rate prior to database lock. After the database lock, changes in PRO scores over time were not presented graphically.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 69 subjects were screened for this trial and 65 subjects were enrolled. Of the 65 enrolled subjects, two subjects were withdrawn before dosing with turoctocog alfa, yielding 63 dosed subjects. Three subjects were withdrawn after dosing; thus 60

subjects completed the trial. Of the 60 subjects completing the trial, 29 were young children (0 - < 6 years) and 31 were older children (6 - < 12 years).

All 63 subjects who were dosed with turoctocog alfa were included in the FAS. The FAS population was equally split between the two age cohorts (31 young children and 32 older children) and consisted of males with severe hemophilia (FVIII activity $\leq 1\%$), with a median age of 6 years old (ranging from 1 to 11 years old) and a median weight of 21.0 kg (ranging from 11.7 to 56.0 kg). The majority of the subjects were White (84%) and the second-largest group was Asian (10%). Nineteen percent (19%) of the subjects were from the US, 14% were from Brazil, 13% were from Russia and 11% were from Turkey, while the remaining 42% of the subjects were distributed between seven other countries.

3.2.3 Statistical Methods

Primary endpoint:

The incidence rate of FVIII inhibitors was reported and a one-sided 97.5% upper confidence limit was provided based on an exact calculation for a binomial distribution. For the calculation of the rate, the numerator included all subjects with inhibitors while the denominator included all subjects with a minimum of 50 exposure days plus any subjects with less than 50 exposure days but with inhibitors. Adequate safety with regard to inhibitors was concluded if the upper one-sided 97.5% confidence limit was below 10.7%. In terms of actual number of inhibitors, applying the success criteria meant that one or fewer inhibitors in the planned 60 subjects (giving a rate of 2% and an upper 97.5% confidence limit of 10.7%) was considered acceptable.

Secondary efficacy endpoints:

- ***Consumption of turoctocog alfa***

Total actual consumption of turoctocog alfa (IU/kg BW) per subject was calculated for prevention (per month and per year) and for treatment of bleeds. Actual consumption of turoctocog alfa (IU/kg BW/bleed) per subject per bleed for treatment of bleeds was calculated as the consumption of turoctocog alfa used from the start of the bleed to the stop of the bleed. The total actual consumption of turoctocog alfa per subject (prevention and treatment of bleeds) was calculated as the sum of the entire consumption of turoctocog alfa.

- ***Prevention***

The annualized bleeding rate was estimated in total and by cause of bleed (spontaneous, traumatic or other) based on a Poisson model allowing for overdispersion. No formal statistical testing was performed. For all subjects, including subjects withdrawn after dosing, the observed number of bleeds and observed time in the trial after the first dose of turoctocog alfa was used as input when estimating the annualized bleeding rate.

In addition, the estimated annualized bleeding rate in total and by cause of bleed, excluding all information more than 72 hours after previous turoctocog alfa dose, was estimated by a Poisson model allowing for overdispersion. The estimated annualized bleeding rate in total and by cause of bleed excluding all information more than 48 hours after previous turoctocog alfa dose was estimated by a Poisson model allowing

for overdispersion. The estimated annualized bleeding rate was also estimated by country and by compliance group.

- ***Treatment of bleeds***

Haemostatic effect of turoctocog alfa when used for treatment of acute bleeds was evaluated according to a predefined four-point scale (none, moderate, good or excellent) and presented using counts and percentages of bleeding episodes. If the haemostatic response was rated as excellent or good, the treatment of the bleed was counted as a success. If the haemostatic response was rated as moderate or none, the treatment was counted as a failure. As a conservative approach, the missing ratings were included as treatment failures.

Furthermore, the haemostatic effect of turoctocog alfa was summarized by cause of bleed (spontaneous, traumatic or other), site of the bleed (central nervous system, joint, gastrointestinal, subcutaneous, muscular or other), classification of the bleed (mild/moderate or severe), time of the bleed (the day was divided into six time intervals, each of four hours), and compliance (good compliance or less compliance), respectively. Details (cause, site, classification and time) of the bleeds were summarized and listed.

The number of infusions of turoctocog alfa administered per bleed was calculated as the number of infusions of turoctocog alfa from start to stop of the bleed.

Secondary safety endpoints:

Evaluation of secondary safety endpoints was based on descriptive statistics.

Categorical data were summarized by frequency tables while continuous data were summarized by the mean, standard deviation (SD), and minimum and maximum value.

3.2.4 Results and Conclusions

The following summarizes the analysis result for Trial 3545(source: report-body.pdf in section 5.3.5.2.3):

Primary safety endpoint:

- No FVIII inhibitors were detected. The one-sided 97.5% upper confidence limit for the inhibitor incidence rate of zero was 6.06%, thus the primary evaluation of adequate safety (upper confidence limit below 10.7%) succeeded. One subject had a positive FVIII inhibitor test (1.3 BU) at Visit 4, however, the results of a second separately drawn sample was negative, meaning that the definition of FVIII inhibitors was not met.
- Since there was no FVIII inhibitors detected, no subgroup analysis by gender, age or race/ ethnicity was conducted.

Secondary safety endpoints:

- A total of 86 AEs were reported for 32 of the 63 (51%) subjects exposed to turoctocog alfa. All AEs were of mild or moderate severity. The most commonly reported AEs were related to dosing (underdose was reported for two subjects [3.2%], incorrect dose administered was reported for one subject [1.6%], overdose was reported for one subject [1.6%] and injection site extravasation was reported for one subject [1.6%]), nasopharyngitis (reported for five subjects [7.9%]) and upper respiratory tract infection (reported for five subjects [7.9%]).

- Two (2) events (incorrect dose administered and contusion) in one subject (1.6%) were evaluated by the investigator to be possibly related to turoctocog alfa. Both events were non-serious and of mild or moderate severity.
- Three (3) serious adverse events (soft tissue injury, gastroenteritis viral and device related infection) were recorded in 3 (4.8%) subjects. All three events were evaluated as unlikely related to turoctocog alfa by the investigator and all patients recovered from their serious adverse events.
- No thromboembolic events or allergic type hypersensitivity reactions occurred during the trial.

Secondary efficacy endpoints:

- Of the 126 reported bleeds, 102 (81.0%) were stopped with one infusion of turoctocog alfa and 18 (14.3%) were stopped with two infusions.
- The estimated annualized bleeding rate (spontaneous and traumatic) was 5.33 bleeds /subject /year. The estimated annualized bleeding rate for spontaneous bleeds was low with a mean rate of 1.69 bleeds/subject/year and a lower rate was seen for young children (0.80 bleeds/subject/year) than for older children (2.49 bleeds /subject/year).
- The success rate for treatment of bleeds was 94.3% (excluding bleeds for which there was no outcome reported). A more conservative approach (considering bleeds for which there was no reported outcome as treatment failures) gave a success rate of 92.1% for treatment of bleeds.

3.3 Trial 3568

3.3.1 Study Design

Study Design and Objectives:

This trial was designed as an extension, multicenter (18 sites), open-label, prospective trial where subjects completing one of the Trials 3543, 3545, 3600 or 3893 could continue treatment with turoctocog alfa. The trial investigated the long-term safety and efficacy of turoctocog alfa in subjects with hemophilia A without inhibitors and a FVIII activity $\leq 1\%$. Furthermore, a sub-trial was designed to provide information on efficacy and safety of turoctocog alfa administered as either bolus or continuous infusion during surgery.

Endpoints:

- (1) Primary safety endpoint: Frequency of development of FVIII inhibitors
- (2) Secondary safety endpoint: Frequency of AEs and SAEs
- (3) Secondary efficacy endpoints:
During preventive regimen: Annualized bleeding rate related to the preventive period; Haemostatic response to turoctocog alfa (none, moderate, good or excellent) in treatment of bleeds
During on-demand regimen: Haemostatic response to turoctocog alfa (none, moderate, good or excellent) in treatment of bleeds
- (4) Primary safety endpoint (surgery sub-trial): Haemostatic effect of turoctocog alfa assessed by evaluation according to a predefined four-point scale (none, moderate, good or excellent)
- (5) Secondary safety endpoints (surgery sub-trial): Frequency of AEs and SAEs

reported during the surgery and post-surgery recovery period

(6) Secondary efficacy endpoints (surgery sub-trial): 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; Hemoglobin level prior to surgery, during, and after surgery (pre-operative, intra-operative and post-operative); Blood product transfusion

Randomization Scheme:

The trial was not randomized.

Blinding:

This was an open-label trial.

Sample Size:

The planned number of subjects to be started on trial product was 145.

Analysis Populations:

All subjects who were dosed with turoctocog alfa as of the cut-off date (November 21, 2011) were included in the FAS on which all the efficacy were planned. The safety analysis set was identical to the FAS.

Protocol Amendment and Deviation:

Several changes are related to the study design and statistical analysis:

(1) Changes prior to database lock: AEs and SAEs were proposed to be reported as rates per 100 subject years, but were reported as rates per subject years of exposure in the final report. The secondary efficacy endpoint for the prevention period was changed from 'Average number of bleeds per month reported during the prevention period' to 'annualized bleeding rate'. In section 17.3.3 of the protocol, the prevention period was specified as related to 'patients on preventive regimen'. The text in the statistical analysis plan was changed to focus on 'time on preventive regimen' rather than 'patients on preventive regimen'.

(2) Changes after database lock: The rate of adverse events was reported per subject year instead of per 100 subject years. Furthermore, as only two subjects were included in the surgery sub-trial as of the cut-off date (21 November 2011) information on the primary and secondary endpoints for the surgery sub-trial was listed only. During the preparation of the clinical trial report it was observed that subject numbers -----

----- (b)(6) ----- were registered as being on an on-demand treatment regimen or on a preventive treatment regimen, but with dosing frequency 'as required'. Eight of these nine subjects had received turoctocog alfa regularly without having bleeds and subject -(b)(6)- had only received one dose at Visit 1, thus the total duration of exposure for this subject was set to zero. It was decided by the trial team to analyze data from these nine subjects together with the group of subjects being on preventive treatment. In addition, one subject (subject number -(b)(6)-) was registered as being on an on-demand treatment regimen between 15 September 2010 and 27 October 2010. As this was a very short period and as the subject had been on preventive treatment prior to this period and returned to preventive treatment after this period, it was also decided by the trial team to analyze data from this subject together with the group of subjects being on preventive treatment. As of the cut-off date, no subjects were therefore considered to be in the on-demand treatment regimen.

3.3.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 189 subjects were enrolled and 187 subjects were dosed with turoctocog alfa as of the cut-off date November 21, 2011.

The population consisted of 187 male patients with severe haemophilia (FVIII activity $\leq 1\%$) and was divided into four age groups: young children (0 - <6 years), older children (6 - <12 years), adolescents (12 - <18 years) and adults (≥ 18 years). The age is defined as the age when the subject entered the first turoctocog alfa trial. Prior to the trial, the mean number of turoctocog alfa infusions per subject was 81 infusions. The majority of subjects were White (83%) and the second-largest group was Asian (11%). The three largest nationalities were US (17%), Serbia (13%) and Brazil (12%), while the remaining 58% of the subjects were distributed among the other 15 countries.

3.3.3 Statistical Methods

FVIII inhibitor development during the trial was summarized and listed. Annualized bleeding rates were estimated based on a Poisson model allowing for overdispersion and no formal statistical testing was performed. The haemostatic response after treatment of a bleed with turoctocog alfa was evaluated on a four-point scale as excellent, good, moderate or none. If the haemostatic effect of treatment of a bleed was rated as excellent or good, the treatment was counted as a success. If the haemostatic effect was rated as moderate or none, the treatment was counted as a failure. Other safety information was summarized using descriptive statistics.

3.3.4 Results and Conclusions

Primary safety endpoint:

- As of the cut-off date (November 21, 2011), no FVIII inhibitors were detected.
- Since there was no FVIII inhibitors detected, no subgroup analysis by gender or race/ethnicity was conducted.

Secondary safety endpoints:

- A total of 178 AEs were reported for 76 (41%) subjects exposed to turoctocog alfa corresponding to an AE rate of 1.7 events per subject year of exposure. Two of these AEs (arthralgia and vomiting) were recorded in two subjects during surgery. The most frequently reported AEs were arthralgia, nasopharyngitis and headache (all with a rate of 0.1 AE per subject year of exposure).
- Three (3) events in two subjects were evaluated by the investigator to be possibly or probably related to turoctocog alfa. All events were non-serious and of mild or moderate severity.
- Of 178 AEs, 42 AEs were reported from 18 subjects with age less than or equal to 16 years, 2 AEs were reported from 2 subjects with age between 16 and 18 years, 102 AEs were reported from 40 subjects with age between 18 and 30 years, and 32 AEs were reported from 16 subjects older than 30 years.
- No thromboembolic events were reported. No events of hypersensitivity against turoctocog alfa were reported.

Secondary efficacy endpoints:

- At the cut-off date, a total of 366 bleeds were reported in 86 of the 187 participating subjects.
- The overall estimated annualized bleeding rate was low (3.54 bleeds/subject/year) ranging from 2.61 bleeds/subject/year in adolescents to 3.71 bleeds/subject/year in adults.
- The overall success rate for treatment of bleeds was 87.2% ranging from 73.9% in older children to 93.8% in adolescents. Of the 366 reported bleeds, 288 (78.7%) were stopped with one infusion of turoctocog alfa, 44 (12.0%) were stopped with two infusions and 34 (9.4%) were stopped with three or more infusions. The success rate during and after surgery was 100% based on two major surgeries.

4. SUMMARY AND CONCLUSIONS

The primary objective of the studies was the evaluation of the safety of turoctocog alfa. No FVIII inhibitors were detected for Trials 3543, 3545 and 3568, and the pre-specified success criteria for safety were met. The protocols did not specify the success criteria to claim efficacy of turoctocog alfa. No formal statistical testing was performed to evaluate the efficacy of the studies, but instead summary statistics were provided. This reviewer defers to the clinical reviewer to decide the efficacy success criteria.

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