

CLINICAL PHARMACOLOGY BLA REVIEW

Division of Hematology
Office of Blood Review & Research

STN 125466/0

Sponsor: Novo Nordisk

Product: Antihemophilic Factor (recombinant), plasma/albumin free (NovoEight) Turoctocog alfa

Indication: Control and prevention of bleeding in patients with hemophilia A

Submission Date: October 16, 2012

Reviewer: Iftekhar Mahmood, Ph. D.

RPM: Leigh Pracht

Through: Basil Golding, M. D.

TABLE OF CONTENTS

Introduction	1
Clinical Pharmacology Labeling Comments	3
Revised Clinical Pharmacology Labeling	7
Recommendations	9

Study 1: A multi-center, multi-national, open-label sequential trial comparing pharmacokinetics and safety of turoctocog alfa and Advate in subjects with hemophilia A ((NN 7008-3522).

10

Study 2: Multi-center, open-label, non-randomized single dose trial investigating the pharmacokinetics of turoctocog alfa in Japanese patients with hemophilia A (NN 7008-3600).

12

Study 3: A multi-center, open-label, non-controlled trial on safety and efficacy of turoctocog alfa in prevention and treatment of bleeds in previously treated patients with hemophilia A (NN7008-3543).

14

Study 4: A multi-center, open-label, non-controlled trial on safety and efficacy of turoctocog alfa in previously treated pediatric patients with hemophilia A.

16

INTRODUCTION

Novo Nordisk's recombinant factor VIII product (turoctocog alfa) is a serum free hemostatic protein where an inactive section of the FVIII molecule has been truncated to provide a

therapeutic compound. Turoctocog alfa is produced in serum-free fermentation culture and formulated without proteins of animal or human origin.

NovoEight [Antihemophilic Factor (Recombinant), Plasma/Albumin-Free] is a human recombinant Factor VIII with a molecular mass of 166 kDa. NovoEight is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line. In culture, the CHO cell line expresses recombinant Factor VIII (rFVIII) into the cell culture medium. The rFVIII is purified from the cell culture medium using a series of chromatography steps. The production process includes two viral inactivation steps, a detergent treatment step and a 20 nanometer virus filtration step. The rFVIII synthesized by the CHO cells has the same biological effects on clotting as native human Factor VIII. NovoEight is formulated as a sterile, non-pyrogenic, white or slightly yellow powder for intravenous injection. The specific activity of NovoEight is approximately (b)(4) IU per milligram of protein.

CLINICAL PHARMACOLOGY LABELING COMMENTS

12.1 Mechanism of Action

Hemophilia is a sex-linked hereditary disorder of blood coagulation due to decreased levels of Factor VIII and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy, the plasma levels of Factor VIII are increased, thereby enabling a temporary correction of the Factor deficiency and correction of bleeding tendencies.

NovoEight temporarily replaces the missing clotting Factor VIII that is needed for effective hemostasis. When infused into a patient with hemophilia, Factor VIII binds to endogenous von Willebrand Factor in the patient's circulation. Activated Factor VIII acts as a co-Factor for activated Factor IX accelerating the conversion of Factor X to activated Factor X. Activated Factor X then converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed.

12.2 Pharmacodynamics

The activated partial thromboplastin time (aPTT) is prolonged in patients with hemophilia A. Treatment with NovoEight normalizes the aPTT over the effective dosing period.

12.3 Pharmacokinetics

All pharmacokinetic studies with NovoEight were conducted in previously treated patients with severe hemophilia A (Factor VIII \leq 1%). The analysis of plasma samples was conducted using both the one-stage clotting assay and the chromogenic assay.

~~A multi-center, randomized and blinded field study has been conducted to evaluate assay performance, activity, and variability of NovoEight in spiked plasma from patients with hemophilia A at different clinical laboratories with the methodology and reagents routinely used in the laboratories. A total of 36 laboratories participated in the study; 33 laboratories used the one stage clotting assay; 5 used the chromogenic assay, and 2 laboratories used both assays. Comparable and consistent estimates of target value were observed for NovoEight.~~

~~—The pharmacokinetic parameters derived from an open label sequential trial comparing the pharmacokinetics of NovoEight and Advate[®] in 22 previously treated patients \geq 12 years of age are listed in Table 6.~~

In a multi-center, multi-national, open-label, single dose pharmacokinetic trial in patients with hemophilia A (Factor VIII activity $<$ 1%), 23 patients received 50 IU/kg of NovoEight intravenously. Two patients were below the age of 18 years (13 and 17 years). The pharmacokinetic parameters of the study are summarized in Table 3.

Table 1: Pharmacokinetics of NovoEight in 20 adult and adolescent patients with severe Hemophilia A (Factor VIII \leq 1%) following a single IV dose of 50 IU/kg

Parameter	Clotting assay	Chromogenic assay
	Mean (SD)	Mean (SD)
Incremental Recovery (IU/mL)/(IU/kg)	0.020 (0.002)	0.020 (0.006)
AUC (IU*h/mL)	14.22 (3.75)	18.70 (5.08)
CL (mL/h/kg)	3.74 (0.95)	2.87 (0.80)
t $\frac{1}{2}$ (h)	10.83 (4.95)	11.96 (9.28)
V _{ss} (mL/kg)	53.43 (10.88)	44.31 (28.17)
C _{max} (IU/mL)	1.07 (0.16)	1.54 (0.29)
MRT (h)	15.43 (6.36)	16.40 (10.14)

Dose: 50 IU/kg NovoEight (single IV dose)

Full analysis set adjusted for dose and product strength and excluding outliers; N=20

In a pharmacokinetic study, 28 pediatric patients with hemophilia A received a single dose of 50 IU/kg NovoEight. There were 14 patients below 6 years of age and 14 patients between 6-<12 years of age. The pharmacokinetic parameters of NovoEight are summarized in Tables 4 and 5 for both age groups.

~~Pharmacokinetic data from single dose administrations of NovoEight in 14 pediatric patients below 6 years of age, and in 14 pediatric patients from 6 to below 12 years of age are listed in Table 4 and 5, respectively.~~

Table 2: Pharmacokinetics of NovoEight in 14 children with Hemophilia A following a single IV dose of 50 IU/kg (0 - < 6 years)

Parameter	Clotting assay	Chromogenic assay
	Mean (SD)	Mean (SD)
Incremental Recovery (IU/mL)/(IU/kg)	0.018 (0.007)	0.022 (0.006)
AUC (IU*h/mL)	9.89 (4.14)	12.21 (4.38)
CL (mL/h/kg)	6.26 (3.73)	4.60 (1.75)
t $\frac{1}{2}$ (h)	7.65 (1.84)	9.99 (1.71)
V _{ss} (mL/kg)	57.30 (26.75)	55.79 (23.71)
C _{max} (IU/mL)	1.00 (0.58)	1.12 (0.31)
MRT (h)	9.65 (2.46)	12.09 (1.88)

Dose: 50 IU/kg NovoEight (single i.v. dose); N=14

Table 5: Pharmacokinetics of NovoEight in 14 children with Hemophilia A following a single IV dose of 50 IU/kg (6 – <12 years)

Parameter	Clotting assay	Chromogenic assay
	Mean (SD)	Mean (SD)
Incremental Recovery (IU/mL)/(IU/kg)	0.020 (0.004)	0.025 (0.006)
AUC (IU*h/mL)	11.09 (3.73)	14.36 (3.48)
CL (mL/h/kg)	5.02 (1.67)	3.70 (1.00)
t _{1/2} (h)	8.02 (1.89)	9.42 (1.52)
V _{ss} (mL/kg)	46.82 (10.62)	41.23 (6.00)
C _{max} (IU/mL)	1.07 (0.35)	1.25 (0.27)
MRT (h)	9.91 (2.57)	11.61 (2.32)

The pharmacokinetic parameters were comparable between younger (0 – < 6 years) and older (6– < 12 years) children. Some variation was observed in the pharmacokinetic parameters of NovoEight between pediatric and adult patients. The mean CL of NovoEight in younger and older children was 67% and 34% higher (based on per kg body weight) than in adults (3.74 mL/h/kg) when using the clotting assay, and 60% and 29% higher than in adults (2.87 mL/h/kg) when using the chromogenic assay. The mean half-life of NovoEight in younger and older children was 29% and 26% shorter than in adults (10.83 hours) when using the clotting assay, and 16% and 21% shorter than in adults (11.96 hours) when using the chromogenic assay. Similar pharmacokinetic findings in children have been reported for other Factor VIII products. (Ref 3-5)

Sponsor: A single dose pharmacokinetic study of turoctocog alfa indicates that clearance increased with increasing age. The clearance of turoctocog alfa in younger children (1-5 years), older children (6-12 years), and adults was 79, 117, and 210 mL/hr, respectively. In children 1-5 years and 6-12 years, the clearance of of turoctocog alfa is about 62% and 44% of adult clearance. Please explain how you will adjust the dose of turoctocog alfa in these two age groups?

~~Table 3 Comparison of Advate[®] and NovoEight pharmacokinetics (Ref 2)~~

Parameter	Advate [®] (50 IU kg ⁻¹) n = 20		NovoEight (50 IU kg ⁻¹) n = 20	
	Mean (SD)	Minimum–maximum	Mean (SD)	Minimum–maximum

Parameter	Advate [®] (50 IU kg ⁻¹) n = 20		NovoEight (50 IU kg ⁻¹) n = 20	
	Mean (SD)	Minimum– maximum	Mean (SD)	Minimum– maximum
Primary PK parameters				
Incremental recovery (IU mL ⁻¹)/(IU kg ⁻¹)	0.019 (0.003)	{0.016; 0.025}	0.019 (0.002)	{0.016; 0.023}
AUC (h*IU mL ⁻¹)	13.03 (4.25)	{6.72; 26.28}	12.97 (3.48)	{7.21; 22.76}
t _{1/2} (h)	11.19 (3.51)	{5.70; 22.11}	10.83 (4.95)	{3.96; 28.19}
Total Cl (mL h ⁻¹)	307.0 (100.2)	{102.7; 543.6}	302.3 (98.12)	{118.6; 520.1}
Weight normalized Cl (mL h ⁻¹ kg ⁻¹)	4.17 (1.20)	{1.90; 7.45}	4.11 (1.06)	{2.20; 6.94}
Secondary PK parameters				
AUC _{last} (h*IU mL ⁻¹)	12.15 (3.29)	{6.57; 21.16}	12.09 (2.66)	{7.12; 17.31}
C _{max} (IU mL ⁻¹)	1.02 (0.13)	{0.88; 1.34}	0.99 (0.15)	{0.80; 1.33}
MRT (h)	15.79 (4.74)	{7.99; 29.51}	15.71 (6.38)	{6.35; 38.14}
C ₍₀₎ (IU mL ⁻¹)	1.11 (0.15)	{0.90; 1.50}	1.04 (0.17)	{0.80; 1.39}
Total V _{ss} (mL)	4466 (801.7)	{3032; 6385}	4284 (748.6)	{3302; 5845}
Weight normalized V _{ss} (mL kg ⁻¹)	61.31 (7.90)	{38.67; 78.25}	59.77 (11.73)	{44.03; 83.77}
Total V _z (mL)	4556 (826.6)	{3138; 6692}	4225 (924.3)	{2574; 5729}
Weight normalized Vz (mL kg ⁻¹)	62.57 (8.20)	{41.37; 83.07}	59.06 (14.68)	{34.79; 89.32}

Incremental recovery: FVIII:C activity 30 min after end of infusion relative to the administered dose.

AUC, area under the plasma concentration curve; t_{1/2}, terminal half life; Cl, clearance; AUC_{last}, AUC from time 0 to the last measurable concentration; C_{max}, maximum concentration; MRT, mean residence time; C₍₀₎, concentration at time 0 (end of infusion); V_{ss}, apparent volume of distribution at steady state; V_z, apparent volume of distribution based on the terminal phase. Table 6 shows the comparison of NovoEight to Advate[®] in PK parameters after a single dose. All parameters for Advate[®] and NovoEight were comparable (see Table 6). There was no significant difference in the rate and extent of availability of Factor VIII in plasma between NovoEight and Advate[®] when administered at the same dose under similar conditions in this study.

Pharmacokinetic data with NovoEight from Previously Untreated Patients (PUPs) are currently not available.

REVISED CLINICAL PHARMACOLOGY LABELING COMMENTS

The applicant has revised the clinical pharmacology labeling section as suggested by the FDA and is as follows:

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Novoeight temporarily replaces the missing clotting factor VIII that is needed for effective hemostasis.

12.2 Pharmacodynamics

The activated partial thromboplastin time (aPTT) is prolonged in patients with hemophilia A. Determination of aPTT is a conventional *in vitro* assay for the biological activity of FVIII. Treatment with Novoeight normalizes the aPTT over the effective dosing period.

12.3 Pharmacokinetics

All pharmacokinetic studies with Novoeight were conducted in previously treated patients with severe hemophilia A (factor VIII \leq 1%). Analysis of plasma samples was conducted using both the one-stage clotting assay and the chromogenic assay.

In a multi-center, multi-national, open-label, single dose pharmacokinetic study, 23 patients with severe hemophilia A received 50 international units/kg of Novoeight intravenously. Two patients were below the age of 18 years (13 and 17 years). The pharmacokinetic parameters for 20 patients who completed the study are summarized in Table 4.

Table 4: Pharmacokinetics of Novoeight in 20 adult and adolescent patients with hemophilia A

Parameter	Clotting assay	Chromogenic assay
	Mean (SD)	Mean (SD)
Incremental Recovery (IU/mL)/(IU/kg)	0.020 (0.002)	0.028 (0.006)
AUC (IU*h/mL)	14.2 (3.8)	18.7 (5.1)
CL (mL/h/kg)	3.74 (0.95)	2.87 (0.80)
t _{1/2} (h)	10.8 (4.9)	12.0 (9.3)
V _{ss} (mL/kg)	53.4 (10.9)	44.3 (28.2)
C _{max} (IU/mL)	1.07 (0.16)	1.54 (0.29)
MRT (h)	15.4 (6.4)	16.4 (10.1)

In a separate pharmacokinetic study, 28 pediatric patients with severe hemophilia A (14 patients were below 6 years of age and 14 patients were between 6 to <12 years of age) received a single dose of 50 international units/kg Novoeight. The pharmacokinetic parameters of Novoeight are summarized in Table 5 for both age groups.

Table 5: Pharmacokinetics of Novoeight in 28 pediatric patients with hemophilia A

Parameters	Clotting Assay		Chromogenic Assay	
	0 to <6 years	6 to <12 years	0 to <6 years	6 to <12 years
	Mean (SD)		Mean (SD)	
Incremental Recovery (IU/mL)/(IU/kg)	0.018 (0.007)	0.020 (0.004)	0.022 (0.006)	0.025 (0.006)
AUC (IU*h/mL)	9.9 (4.1)	11.1 (3.7)	12.2 (4.4)	14.4 (3.5)
CL (mL/h/kg)	6.26 (3.73)	5.02 (1.67)	4.60 (1.75)	3.70 (1.00)
t _{1/2} (h)	7.7 (1.8)	8.0 (1.9)	10.0 (1.7)	9.4 (1.5)
V _{ss} (mL/kg)	57.3 (26.8)	46.8 (10.6)	55.8 (23.7)	41.2 (6.0)
C _{max} (IU/mL)	1.00 (0.58)	1.07 (0.35)	1.12 (0.31)	1.25 (0.27)
MRT (h)	9.7 (2.5)	9.9 (2.6)	12.1 (1.9)	11.6 (2.3)

The pharmacokinetic parameters were comparable between younger (0 to < 6 years) and older (6 to < 12 years) children. The mean clearance of Novoeight in younger and older children was 67% and 34% higher (based on per kg body weight) than in adults (3.74 mL/h/kg) when using the clotting assay, and 60% and 29% higher than in adults (2.87 mL/h/kg) when using the chromogenic assay. The mean half-life of Novoeight in younger and older children was 29% and 26% shorter than in adults (10.8 hours) when using the clotting assay, and 16% and 21% shorter than in adults (12 hours) when using the chromogenic assay.

RECOMMENDATION

The pharmacokinetic studies submitted by the applicant are well designed and the results of these studies are acceptable. The applicant has revised the clinical pharmacology labeling as suggested by the FDA. From clinical pharmacology perspective, Novoeight should be approved for commercial use in patients with hemophilia A for control and prevention of bleeding.

Iftexhar Mahmood, Ph. D.
Clinical Pharmacology Reviewer
Division of Hematology
Office of Blood Review & Research

Basil Golding, M. D.
Division Director, Division of Hematology
Office of Blood Review & Research

Study #1

Study Title: A multi-center, multi-national, open-label sequential trial comparing pharmacokinetics and safety of turoctocog alfa and Advate in subjects with hemophilia A ((NN 7008-3522)).

This was a multi-center, multi-national, open-label, single dose pharmacokinetic and safety, trial using a sequential design in non-bleeding patients with hemophilia A (Factor VIII activity <1%). There were 23 male patients (22 Caucasians and one Hispanic) in this trial and the mean age was 22 years (13-54 years). Two patients were below the age of 18 years (13 and 17 years).

The primary objective of the study was to evaluate and compare the pharmacokinetic profiles of intravenously administered recombinant FVIII (turoctocog alfa) and Advate in non-bleeding hemophilia A patients without inhibitors. The secondary objective of the trial was to evaluate the safety of turoctocog alfa in non-bleeding hemophilia A patients without inhibitors.

The Patients received Advate at a dose of 50 IU/kg body weight in the first session and subsequently (following a washout period of 4 days) turoctocog alfa at a dose of 50 IU/kg body weight in the second session. The duration of trial participation for each patient was approximately 4 weeks. The total duration of the trial was estimated to be 6 months.

Blood samples for pharmacokinetic analysis were collected pre-dose, then at 15 and 30 minutes, 1, 4, 8, 12, 24 and 48 hours post administration of trial products. Pharmacokinetic assessments were based on FVIII activity. The FVIII activity was determined using a one-stage clotting assay (clotting assay) and a chromogenic substrate assay (chromogenic assay). In both assays, the dose/activity of turoctocog alfa was expressed in International Units (IU). One IU of Factor VIII activity is equivalent to the quantity of Factor VIII in 1 mL of normal human plasma. The lower limit of quantification (LLOQ) was 0.0125 IU/mL for both assays. Pharmacokinetic parameters were estimated by non-compartmental analysis. Pharmacokinetic parameters of FVIII and advate are summarized in Table 1 and Figure 1.

It should be recognized that the activity assays measure the pharmacodynamic activity and is considered an indirect measure of drug concentration. However, for coagulation factors, it is common practice to apply activity based assays in the assessment of pharmacokinetic properties and in the pharmacokinetic calculations they are regarded as concentrations and are used to calculate pharmacokinetic parameters.

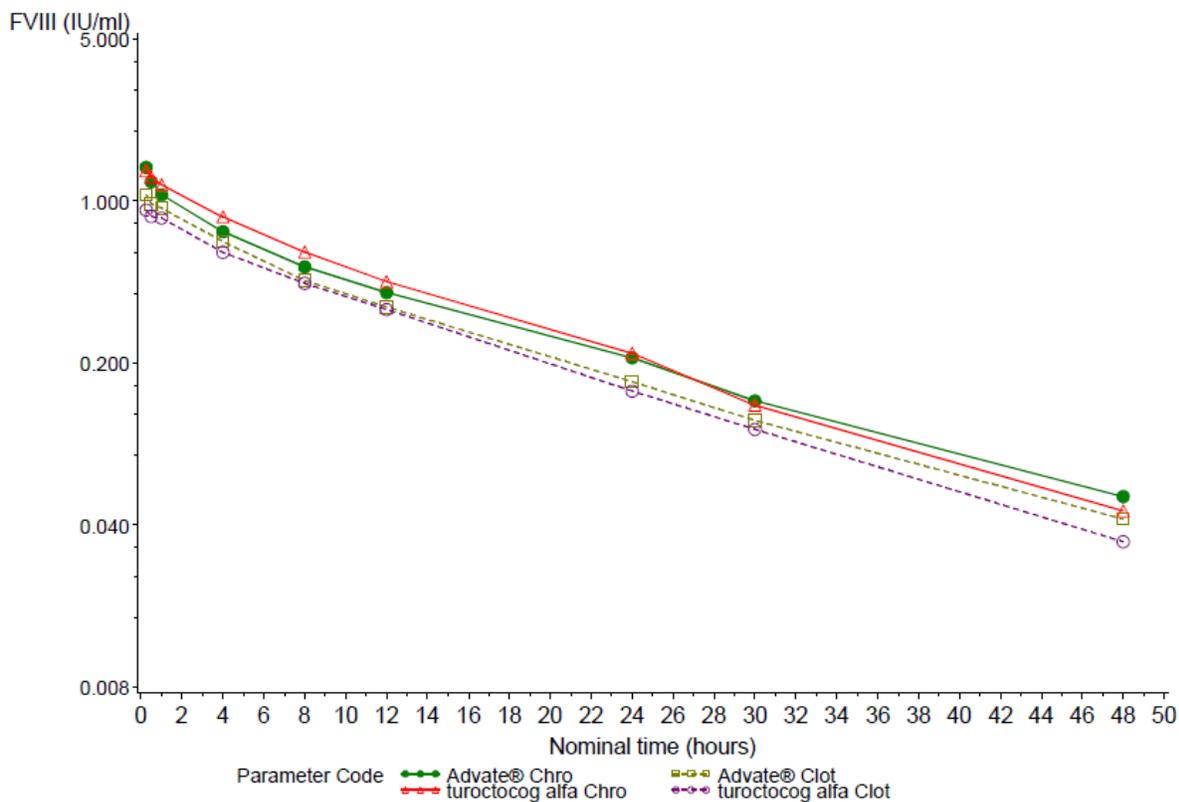
The actual dose administered deviated from the planned dose in some patients. In addition, the actual strengths of trial products deviated from the labeled strengths. The 1500 IU/vial Advate products used for pharmacokinetic assessments included 1505 IU/vial and 1622 IU/vial and the 2000 IU/vial of turoctocog alfa included 1944 IU/vial. When corrected for actual strength of trial products (i.e., IU/vial) the median administered dose of Advate was 54.0 IU/kg and the median dose of turoctocog alfa was 45.2 IU/kg.

The pharmacokinetic parameters of FVIII and advate are shown in Table 1 and concentration-time plot of FVIII and advate is shown in Figure 1. Overall, pharmacokinetics of FVIII were comparable with the pharmacokinetics of advate. Ninety percent confidence interval on log transformed AUC indicated that the confidence interval was within 0.80 to 1.25, indicating that FVIII and advate were bioequivalent.

Table 1
Pharmacokinetic parameters for FVIII and advate estimated by clotting and chromogenic assay methods (Adjusted for actual dose and product strength)

Parameters	Clotting Assay		Chromogenic Assay	
	FVIII	Advate	FVIII	Advate
AUC (IU*hr/mL)	13.6 ± 4.1	12.7 ± 4.3	18.7 ± 5.1	14.9 ± 4.0
CL (mL/hr)	295 ± 115	316 ± 106	210 ± 67	264 ± 88
Half-life (hrs)	11 ± 5	11 ± 3	12 ± 9	12 ± 4
V _{ss} (mL)	3984 ± 775	4428 ± 818	3149 ± 1773	4037 ± 991
Incremental recovery	0.019 ± 0.004	0.018 ± 0.003	0.028 ± 0.006	0.023 ± 0.004

Figure 1: Concentration-time plot of FVIII and advate estimated by clotting and chromogenic assay methods (log scale)



Study #2

Study Title: Multi-center, open-label, non-randomized single dose trial investigating the pharmacokinetics of turoctocog alfa in Japanese patients with hemophilia A (NN 7008-3600).

The primary objective of this study was to evaluate the pharmacokinetics of intravenously administered turoctocog alfa to Japanese patients with hemophilia A without inhibitors in a non-bleeding state. The secondary objective was to evaluate the safety of turoctocog alfa in these patients.

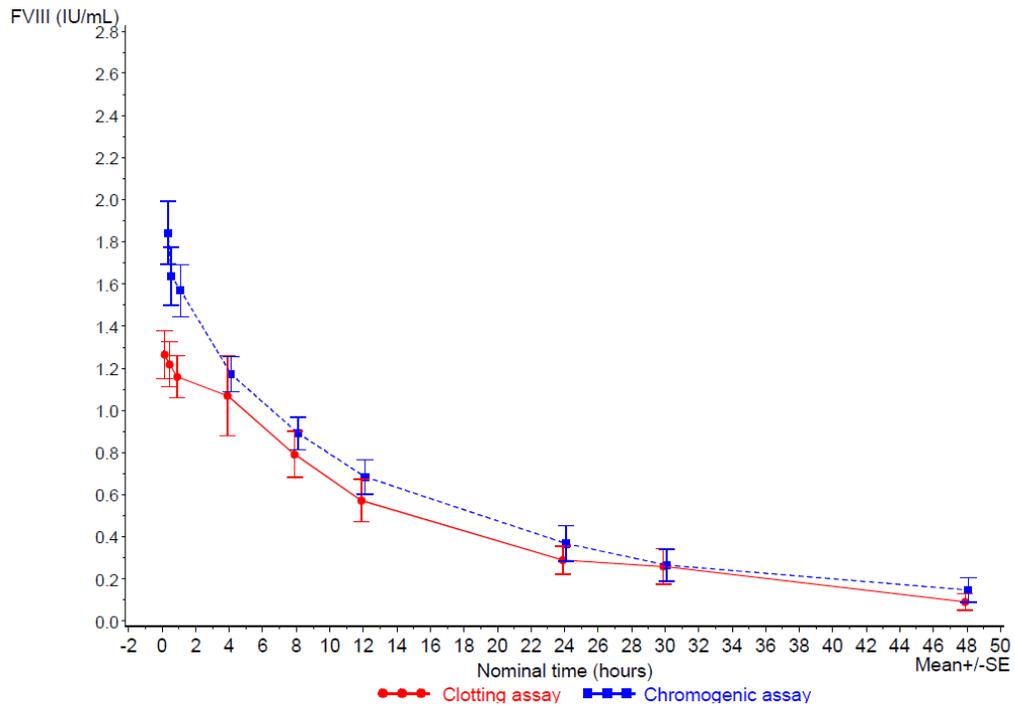
This was a phase I, multi-center, open-label, non-randomized single-dose trial investigating the pharmacokinetics of turoctocog alfa in Japanese patients with hemophilia A. Seven patients were screened and 6 patients completed the trial and were included in the pharmacokinetic analyses. The patients were Japanese males with severe hemophilia A, with a mean age of 33 years (ranging from 19 to 46 years). The mean body weight was 66.5 kg (ranging from 39.6 to 107.0 kg). The patients received a single intravenous turoctocog alfa dose of 50 ± 5 IU/kg. Blood samples for pharmacokinetic study were drawn prior to dosing and at intervals up to 48 hours after administration of turoctocog alfa. The concentrations of turoctocog alfa were measured by clotting and chromogenic assays. The pharmacokinetic parameters estimated by non-compartmental analysis are summarized in the Table 1. The chromogenic assay produced higher concentrations of turoctocog alfa than the clotting assay (Figure 1). As a result, the clearance of turoctocog alfa was slower and half-life was longer by chromogenic assay than the clotting assay.

Pharmacokinetic parameters of turoctocog alfa in Japanese patients with hemophilia A

Parameters	Clotting Assay	Chromogenic Assay
# of subjects	6	6
AUC (hr x IU/mL)	23.1 ± 10.8	29.4 ± 13.2
Clearance (mL/hr)	162 ± 65	124 ± 47
Half-life (hrs)	12.6 ± 5.1	15.5 ± 6.8

The clearance of turoctocog alfa is slower (almost 45%) in Japanese patients with hemophilia A than the Caucasian patients.

Figure 1
Mean concentration-time plot of turoctocog alfa in
Japanese patients with hemophilia A



Study #3

Study Title: A multi-center, open-label, non-controlled trial on safety and efficacy of turoctocog alfa in prevention and treatment of bleeds in previously treated patients with hemophilia A (NN7008-3543).

The trial was designed as a multi-center, multi-national (48 sites in 15 countries), open-label, single-arm efficacy and safety trial in patients with hemophilia A with a FVIII activity $\leq 1\%$. The trial had three parts:

Part A included patients who completed the pharmacokinetic trial (NN7008- 3522)

Part B included patients who participated in the present trial (NN7008-3543) and who did not participate in the pharmacokinetic trial (NN7008-3522)

Part C included patients from part A or part B undergoing surgical procedures

The pharmacokinetic study was only conducted in part A therefore; this review summarizes the study from Part A. The study is basically a comparative study comparing the pharmacokinetics of turoctocog alfa after first dose and then after preventive dosing for 3-6 months. The pharmacokinetic profiles after the first injection of turoctocog alfa, obtained in Trial 3522 (study #1 in this review) were compared with the results obtained after 3-6 months of preventive dosing with turoctocog alfa in Trial 3543.

There were 22 subjects (20 adults and 2 adolescents >12 years of age) with severe hemophilia in the PK study 3543. A wash-out period of ≥ 4 days prior to the pharmacokinetic study was applied. A single dose of 50 IU/kg of turoctocog alfa was given to each patient who was enrolled in the pharmacokinetic study. Only patients with evaluable pharmacokinetic profiles in both trials were included in the comparison. The patients received 36-65 doses of turoctocog alfa prior to the pharmacokinetic study in Trial 3543. Patients eligible for part A or part B of the trial received bleeding preventive treatment with turoctocog alfa at a dose of 20-40 IU/kg every second day or 20-50 IU/kg three times weekly. It should be however, noted that PK study was conducted after 36-65 doses of turoctocog alfa at 50 IU/kg.

Blood samples for PK study were taken at 15 and 30 minutes, 1, 4, 8, 12, 24 and 48 hours post administration. The FVIII activity was determined using a one-stage clotting assay (clotting assay) and a chromogenic substrate assay (chromogenic assay). The comparative analysis consisted of 15 patients because the sponsor considered the remaining 7 subjects as outliers. The results of this study along with the PK parameters obtained from study 3522 are shown in Table 1 and Figure 1.

The individual pharmacokinetic profiles showed that no patients had lower FVIII activity following 3-6 months of preventive dosing (Trial 3543) compared to the first dosing with turoctocog alfa (Trial 3522). Furthermore, the pharmacokinetics of FVIII were comparable between the first dose and after 3-6 months of dosing.

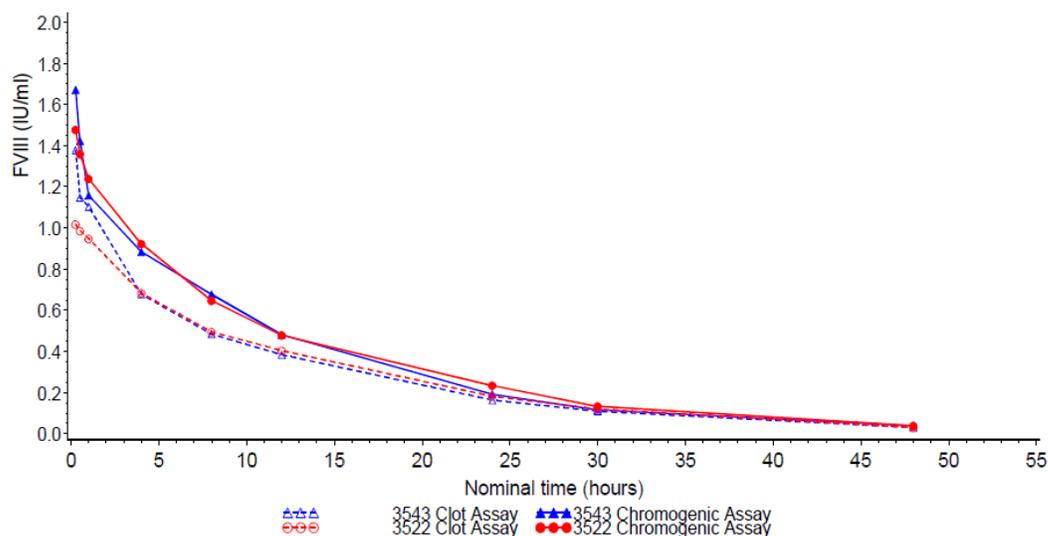
Table 1

Comparison of pharmacokinetic parameters (dose-adjusted) of turoctocog alfa after first dose (Trial 3522) and after preventive dosing for 3-6 months (Trial 3543) to adult and adolescent patients with hemophilia A

	Clotting assay		Chromogenic assay	
	Trial 3522 Mean (SD)	Trial 3543 Mean (SD)	Trial 3522 Mean (SD)	Trial 3543 Mean (SD)
Inc. recovery (IU/mL)/(IU/kg)	0.020 (0.002)	0.023 (0.003)	0.027 (0.005)	0.028 (0.004)
AUC (IU*h/mL)	13.87 (2.68)	13.90 (3.63)	17.65 (3.55)	16.93 (5.26)
Total CL (mL/h)	269.7 (75.57)	284.4 (91.82)	213.0 (57.99)	238.9 (84.64)
t _{1/2} (h)	10.47 (2.34)	10.50 (5.19)	9.47 (2.38) ^a	8.65 (2.09)
V _{ss} (mL) (total)	3576.7 (589.8)	3412.4 (702.9)	2814.8 (883.9)	2806.6 (783.6)
C _{max} (IU/mL)	1.03 (0.11)	1.40 (0.60)	1.50 (0.21)	1.70 (0.71)
MRT (h)	13.79 (2.53)	12.89 (3.52)	13.82 (4.70)	12.39 (2.68)

Dose: 50 IU/kg turoctocog alfa (single i.v. dose); N=15

Figure 1: Mean profiles of FVIII activity (dose-adjusted) for turoctocog alfa after first dose (Trial 3522) and after preventive dosing for 3-6 months (Trial 3543) in adult and adolescent patients with hemophilia A



Dose: 50 IU/kg turoctocog alfa (single i.v. dose); N=15

Study #4

Study Title: A multi-center, open-label, non-controlled trial on safety and efficacy of turoctocog alfa in previously treated pediatric patients with hemophilia A.

The objectives of this study were to evaluate safety and pharmacokinetics of turoctocog alfa in previously treated children with hemophilia A. This was a multi-center, multi-national, non-controlled, open-label, safety, efficacy and pharmacokinetic trial in previously treated pediatric patients with hemophilia A and at least 50 exposure days (EDs) to their previous FVIII product. Patients with severe hemophilia A (FVIII \leq 1%) without inhibitors below 12 years of age in a non-bleeding state were included in the trial. The trial comprised a pharmacokinetic part and a clinical part. The trial was planned to comprise at least 50 completed patients in two age cohorts: one cohort including 25 small children (0-6 years) and one cohort including 25 older children (6- \leq 12 years).

The pharmacokinetic study of a single dose of turoctocog alfa in children (0-<12 years) with hemophilia A consisted of two age groups; 0-6 years and 6-<12 years. Each age group consisted of 14 children. The mean age of the younger children was 3.7 years (range 1-5 years) and the mean age of the older children was 8.2 years (range 6-11 years).

Patients attended a screening visit (Visit 1) in order to assess their eligibility. The first patients enrolled in the trial (at least 13 patients from each age cohort) were enrolled in the pharmacokinetic part of the trial and underwent pharmacokinetic sessions at Visit 2 and Visit 3. At Visit 2, the pharmacokinetic profile of the patients' previous FVIII product was investigated and at Visit 3 the pharmacokinetic profile of turoctocog alfa was assessed. An exception was patients who had an evaluation of the terminal half-life of their previous FVIII product within the last year with at least three time points. These patients underwent the evaluation part of Visit 2 only. Upon completion of the pharmacokinetic sessions the patients initiated preventive treatment with turoctocog alfa from Visit 3 to Visit 8. In the clinical part of the trial, preventive treatment was initiated at Visit 2.

Each patient participating in the pharmacokinetic part of the trial, received one dose of previous FVIII product at Visit 2 (except patients with available evaluation of terminal half-life within the last year) and one dose of turoctocog alfa at Visit 3. The dose level of each product was 50 IU/kg \pm 5 IU/kg and both products were administered intravenously via a bolus injection (2 mL/min). This administration was performed at the clinic.

Visit 2: *Patients participating in the pharmacokinetic part of the trial:* pharmacokinetic session – only for patients not having terminal half-life data for previous product: a single dose of previous FVIII product was administered. Blood samples for determination of FVIII activity were collected at 30 minutes, 10, 24, and 30-48 hours after dosing. The visit lasted 2 days.

Visit 3: *Patients participating in the pharmacokinetic part of the trial:* pharmacokinetic session: a single dose of turoctocog alfa was administered. Blood samples for determination of FVIII

activity were collected at 30 minutes, 1, 4, 10, 24, and 48 hours after dosing. The visit lasted 3 days.

The pharmacokinetic analysis was based on FVIII activity determined by two assays; a clotting assay and a chromogenic assay. The analysis of plasma FVIII activity was performed at a central laboratory. The pharmacokinetic parameters were calculated using standard non-compartmental methods normalized to planned dose. The analysis was done by multiplying individual plasma FVIII activity levels by (planned dose)/(actual dose) and estimating the pharmacokinetic parameters using these numbers. The actual samplings points were used in the calculation of pharmacokinetic parameters. The pharmacokinetic parameters of turoctocog alfa in children are shown in Tables 1 and 2. Concentration-time plots of turoctocog alfa in children are shown in Figures 1-2. The pharmacokinetics of previous Factor VIII product and turoctocog alfa in children were comparable

Table 1: Single-dose pharmacokinetics of turoctocog alfa in children (1-5 years) with hemophilia A

Trial 3545	Clotting assay	Chromogenic assay
	Mean (SD)	Mean (SD)
Incremental recovery (IU/mL)/(IU/kg)	0.018 (0.007)	0.022 (0.006)
AUC (IU*h/mL)	9.89 (4.14)	12.21 (4.38)
Total CL (mL/h) (total)	107.6 (75.00)	79.21 (36.18)
Weight-normalised CL (mL/h/kg)	6.26 (3.73)	4.60 (1.75)
t _{1/2} (h)	7.65 (1.84)	9.99 (1.71)
V _{ss} (mL/kg)	57.30 (26.75)	55.79 (23.71)
C _{max} (IU/mL)	1.00 (0.58)	1.12 (0.31)
MRT (h)	9.65 (2.46)	12.09 (1.88)

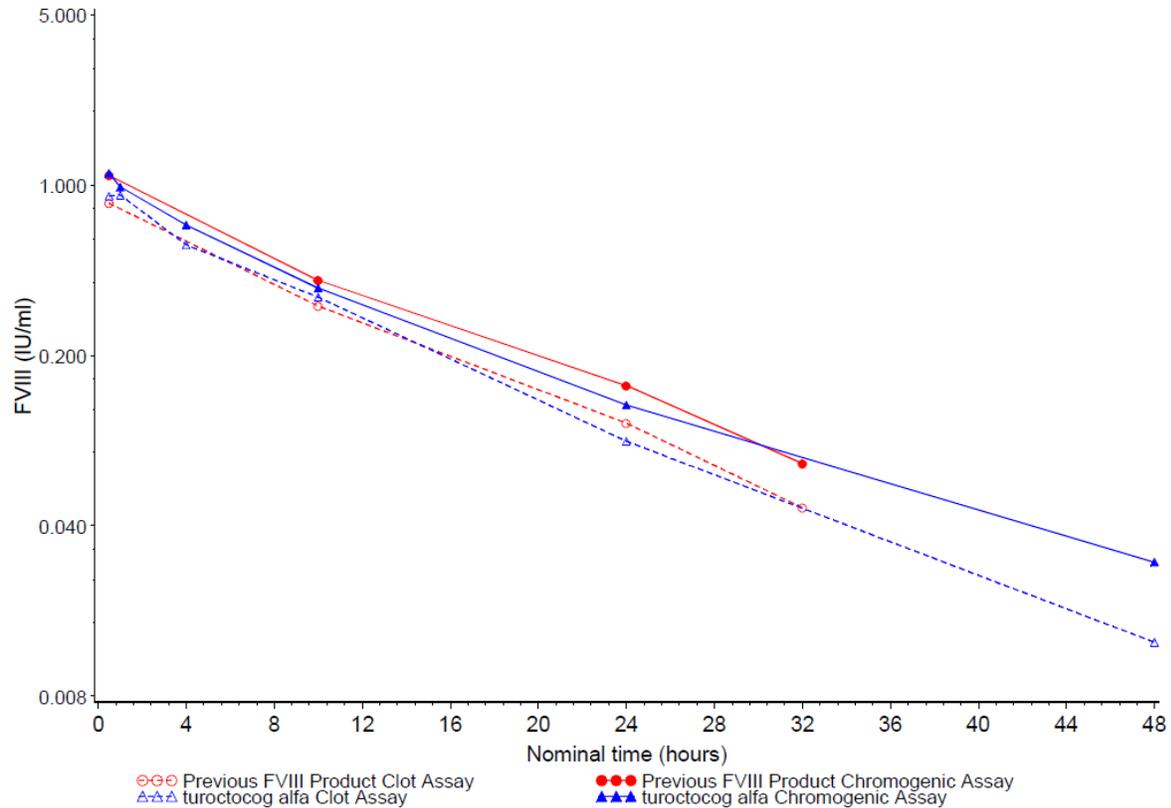
Dose: 50 IU/kg turoctocog alfa (single i.v. dose); N=14

Table 2: Single-dose pharmacokinetics of turoctocog alfa in children (6-<12 years) with hemophilia A

Trial 3545	Clotting assay	Chromogenic assay
	Mean (SD)	Mean (SD)
Incremental recovery (IU/mL)/(IU/kg)	0.020 (0.004)	0.025 (0.006)
AUC (IU*h/mL)	11.09 (3.73)	14.36 (3.48)
Total CL (mL/h)	161.2 (73.48)	117.4 (46.30)
Weight-normalised CL (mL/h/kg)	5.02 (1.67)	3.70 (1.00)
t _{1/2} (h)	8.02 (1.89)	9.42 (1.52)
V _{ss} (mL/kg)	46.82 (10.62)	41.23 (6.00)
C _{max} (IU/mL)	1.07 (0.35)	1.25 (0.27)
MRT (h)	9.91 (2.57)	11.61 (2.32)

Dose: 50 IU/kg turoctocog alfa (single i.v. dose); N=14

Figure 1: Mean concentration-time data of previous Factor VIII product and turoctocog alfa in children 0-6 years of age (log scale)

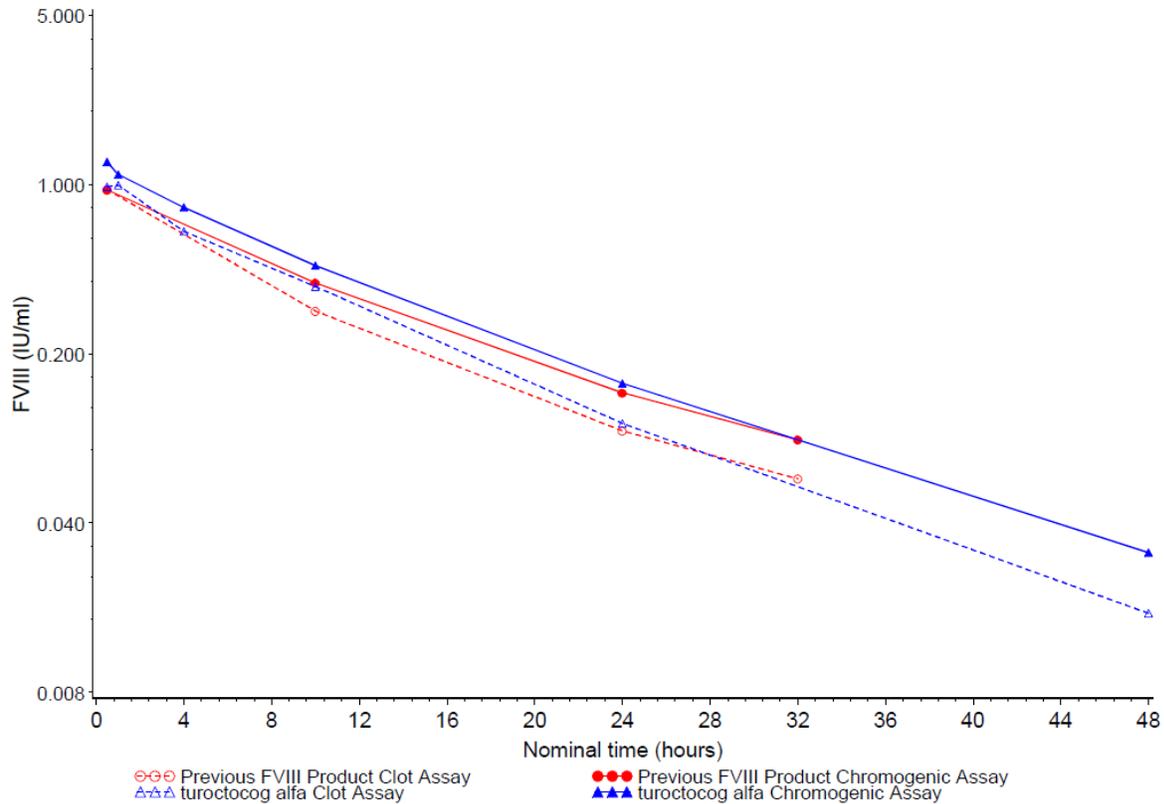


Comparison of turoctocog alfa PK among younger children, older children, and adults

Chromogenic Assay: A single dose pharmacokinetic study of turoctocog alfa indicated that clearance increased with increasing age. The clearance of turoctocog alfa in younger children (1-5 years), older children (6-12 years), and adults was 79, 117, and 210 mL/hr, respectively. The half-life of turoctocog alfa was comparable between younger and older children but it was about 2 hours longer in adults than children. Slightly longer half-life of turoctocog alfa in adults than children is of no clinical significance.

Clotting Assay: A similar pattern was seen with clotting assay. An increased clearance with increasing age and slightly longer half-life in adults than children was noted.

Figure 2: Mean concentration-time data of previous Factor VIII product and turoctocog alfa in children 6-11 years of age (log scale)



Pharmacokinetic parameters derived from the chromogenic assay versus clotting assay:

All pharmacokinetic parameters were estimated based on the concentrations of FVIII using both chromogenic and clotting assays. The mean FVIII activity measured after administration of turoctocog alfa was generally higher using the chromogenic assay compared to the clotting assay. Based on pharmacokinetic data from all trials included in the pharmacokinetic assessment of turoctocog alfa, mean ratios of key pharmacokinetic parameters (AUC, C_{max} and incremental recovery) derived from chromogenic assay versus the clotting assay were approximately 1.3.