19 September 2013
EMA/612026/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

NovoEight

International non-proprietary name: Turoctocog alfa

Procedure No. EMEA/H/C/002719/0000

Note

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

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List of abbreviations

ALT	alanine aminotransferase
APC	Activated Protein C
APTT	Activated Partial Thromboplastin Time
AUC	Area under the activity versus time curve
AUC_{0-24h}	AUC from zero hours to 24 hours
$AUC_{0-\infty}$	AUC from zero hours to infinity
BHT	butylated hydroxytoluene
BU	Bethesda Unit
BW	body weight
CI	confidence interval
Cmax	Peak activity
CHO	Chinese hamster ovary
CL	Clearance
COA	Chromogenic activity assay
CV	coefficient of variation
ED	exposure days
ED50	effective dose 50
ELISA	Enzyme-Linked Immuno Sorbent Assay
FIXa	Activated Coagulation Factor Nine
FVIII	coagulation factor VIII
FVIIIa	Activated Coagulation Factor Eight
FVIII	Coagulation Factor Eight
FX(a)	(Activated) Coagulation Factor Ten
GLP	Good Laboratory Practice
HC	Heavy chain
HCV	hepatitis C virus
HIV	human immunodeficiency virus
h(rs)	hour(s)
I^{125}	Iodine125
ICH	International Conference on Harmonisation
i.v.	intravenous (ly)
IU	International Unit
IVR	in vivo recovery
kDa	Kilo Dalton
kg	Kilogram
KO	Knock Out
L	Litre
LC	Light Chain
LLOQ	Lower Limit of Quantification
mAb(s)	Monoclonal antibody (-ies)
µCi	Micro Curie
µg	Microgram
MA	marketing authorization

MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	minute
ml	Millilitre
mm	Millimetre
MRT	Mean Residence Time
N8	Turoctocog alfa
N/A	Not applicable
NaCl	Sodium Chloride
NCA	Non-Compartmental Analysis
NN7008	Turoctocog alfa (rFVIII)
NOAEL	No Observed Adverse Effect Level
NQ	Not quantified
NS	Not sectioned
PD	Pharmacodynamic(s)
PIP	paediatric investigation plan
PK	Pharmacokinetic(s)
PTP	previously treated patient
PUP	previously untreated patient
r	recombinant
rFVIII	recombinant human coagulation factor VIII
RIA	Radioimmunoassay
SD	Standard Deviation
SDS-PAGE	Sodium Dodecyl Sulfate PolyAcrylamide Gel Electrophoresis
SPC	summary of product characteristics
SPR	Surface Plasmon Resonance
$t_{½}$	Terminal half-life
TEG	thromboelastography
VBS	Visual Bleeding Score
V_{ss}	Volume of distribution at steady-state
vWF	Von Willebrand Factor
WBCT	Whole Blood Clotting Time

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novo Nordisk A/S submitted on 15 October 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for NovoEight, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication, treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that turoctocog alfa was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0150/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0150/2012 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance turoctocog alfa contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 21 January 2010, 20 May 2010 and 17

August 2010. The Scientific Advice pertained to quality and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Andrea Laslop

- The application was received by the EMA on 15 October 2012.
- The procedure started on 21 November 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 February 2013.
- The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 February 2013.
- During the meeting on 21 March 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 March 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 May 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 June 2013.
- During the CHMP meeting on 25 July 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 August 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 28 August 2013.
- During the meeting on 16-19 September 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to NovoEight.

2. Scientific discussion

2.1. Introduction

Haemophilia A is a recessive X-linked congenital bleeding disorder, caused by mutation in the coagulation factor eight (FVIII) gene on the long arm of the X-chromosome. The incidence of haemophilia A is approximately 1 in 5,000 males. Patients with haemophilia A lack or have a reduced production of FVIII, or they produce biochemically defective FVIII molecules.

Haemophilia A is classified as 'severe (<1%)', 'moderate (1−5%)' or 'mild (>5%)' according to the plasma activity of FVIII. With a deficiency or absence of FVIII, the activation of coagulation factor ten (FX) becomes severely impaired, and consequently, the thrombin burst becomes delayed and insufficient for normal haemostasis. Replacing the endogenous FVIII acts as an important co-factor in the activation of FX in the human coagulation cascade leads to thrombin generation and the formation of a stable haemostatic plug. The slow clot formation in patients with haemophilia A results in a fragile haemostatic plug that is easily dissolved by normal fibrinolytic activity, leading to impaired haemostasis, prolonged bleeds and re-bleeds. Recurrent bleeds in the same location, most commonly a weight-bearing joint, lead to chronic arthropathy, muscular atrophy and deformities. Treatment of bleeds as they manifest may delay this process, but does not prevent it.

As the human immunodeficiency virus (HIV) and hepatitis C virus (HCV) epidemics have subsided, the most serious complication to haemophilia treatment is development of neutralising antibodies against FVIII (inhibitors). Inhibitors develop in as many as 24% of patients with severe haemophilia A.

Primary prophylaxis with regular FVIII injections initiated at an early age of life is regarded as the optimal care for children with severe haemophilia A and according to the World Federation of Hemophilia, prophylaxis must be the goal of all haemophilia care programmes until a cure is available.

Novo Nordisk has developed a human recombinant factor VIII (rFVIII) (international nonproprietary name: turoctocog alfa), within the pharmacological class 'anti-haemophilia factors'. The molecule is produced in Chinese hamster ovary (CHO) cells and consists of a heavy chain of 87 kiloDalton (kDa), including a 21 amino acid residue truncated B-domain, and a light chain of 79 kDa. The two chains are held together by non-covalent interactions. The CHO cell culture medium is without serum- or animal-derived components. The trial product, turoctocog alfa, was developed in order to increase treatment options for patients with haemophilia A.

The clinical development program for turoctocog was conducted between March 2009 and November 2011 to obtain MA in the European Union and other markets including the US and was based on current relevant clinical guidelines. During the development, the guideline on the clinical investigation of recombinant factor VIII and IX products was under revision. In 2007, CPMP/BPWG/1561/99 rev.1 was published for consultation. In this draft, severe haemophilia A was defined as factor VIII ⩽1%. In the meantime, it was decided to provide separate guidance documents for FVIII and FIX products. Therefore, in July 2009, the guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (EMEA/CHMP/BPWP/144533/2009) was published for consultation, and in 2011 the finished guidance was published, coming into effect in February 2012. In this guideline, severe haemophilia A was defined as factor VIII <1% in accordance with the definition by the World Federation of Hemophilia.

Current options for recombinant FVIII replacement therapy in haemophilia A include Advate and Recombinate (Baxter), Kogenate FS/Kogenate Bayer (Bayer) and Xyntha/ReFacto AF (Pfizer). All products have a similar efficacy profile.

Novo Nordisk A/S applied for the following indication: Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

The product was presented as a powder and solvent for solution for injection 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU, 3000 IU.

2.2. Quality aspects

2.2.1. Introduction

The turoctocog alfa drug substance is a recombinant glycoprotein that is secreted by a genetically modified Chinese Hamster Ovary (CHO) cell line.

The turoctocog alfa molecule is a polypeptide containing a heavy chain of 87 kDa and a light chain of 79 kDa held together by non-covalent interactions.

Turoctocog alfa is expressed as a single chain where heavy and light chains are connected by a truncated B-domain of 21 amino acids. Once activated by thrombin cleavage, the resulting rFVIIIa has the same structure as endogenous FVIIIa. The posttranslational modifications of turoctocog alfa include eight disulfide bridges, six tyrosine sulfations and seven glycosylation sites.

The drug product is a powder for solution for injection. Turoctocog alfa contains no preservatives and, after reconstitution with 0.9% sodium chloride solution, is intended to be administered by intravenous injection.

Turoctocog alfa drug product is provided as a sterile non-pyrogenic cake in 5 mL glass vials closed with rubber stoppers. The present application includes six nominal drug product strengths: 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU and 3000 IU.

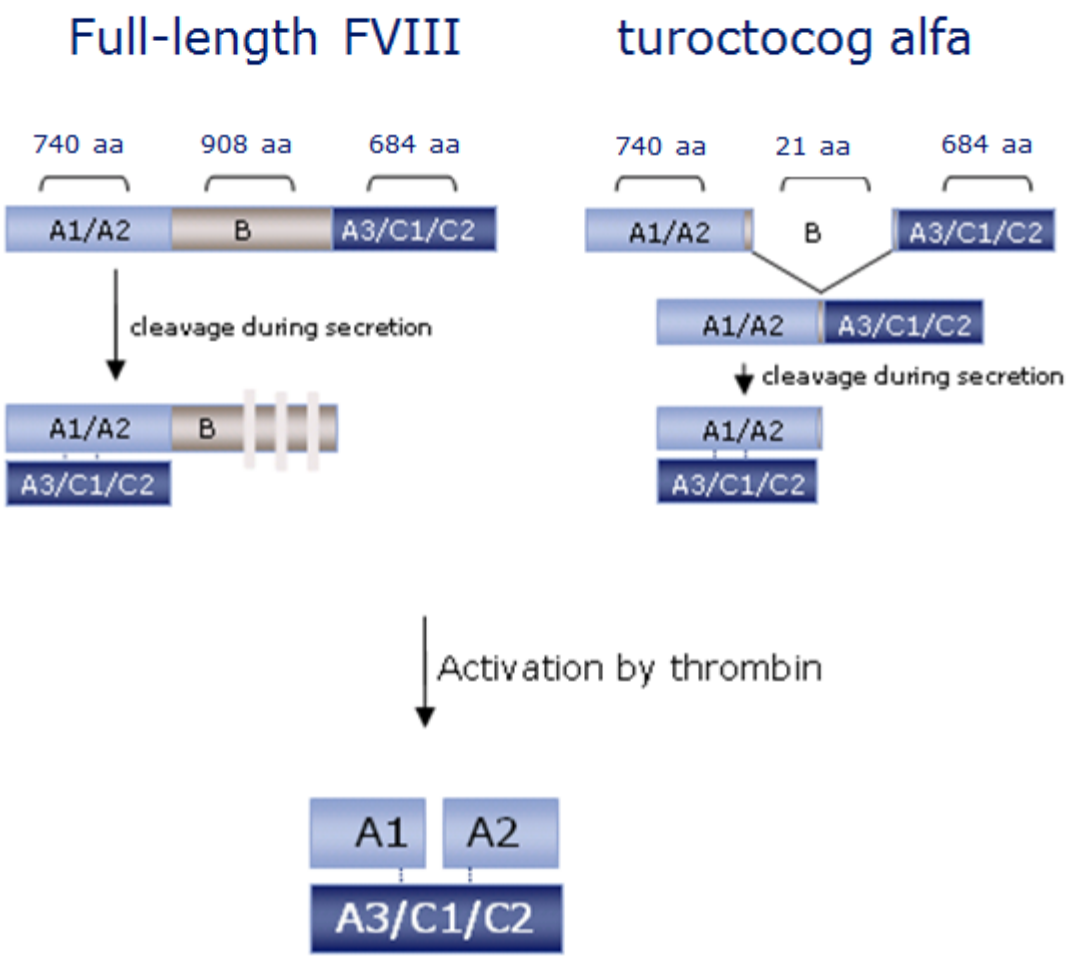
2.2.2. Active Substance

New active substance status

Turoctocog alfa is produced in Chinese hamster ovary cells. The molecule consists of a heavy chain of 87 kDa including a 21 amino acid residue truncated B-domain and a light chain of 79 kDa. The two chains are held together by non-covalent interactions. Two variants of the heavy chain are present in the purified product, namely with and without the B-domain linker attached. This linker is removed upon thrombin activation of turoctocog alfa rendering the activated turoctocog alfa (FVIIIa) molecule similar to FVIIIa derived from FVIII with a complete B-domain (Figure 1).

The amino acid sequence of NovoEight is different to other FVIII products currently authorised.

Although intensively studied, the B-domain does not seem to be required for FVIII function and stability as FVIII molecules with large B-domain truncations (e.g. turoctocog alfa) or no B-domain have full biological activity. For FVIII to be an effective cofactor for FIXa, activation to FVIIIa by thrombin is necessary; a reaction that results in the formation of a heterotrimer composed of the A1, A2 domains (HC) and A3, C1 and C2 domains (LC) and as seen in Figure 1. Regardless of the B-domain, the structure of the activated form (FVIIIa) is the same.



Based on the review of data on the quality properties of the active substance, indicating that turoctocog alfa is neither a full-length nor a B-domain deleted FVIII, but a new B-domain truncated variant of the human coagulation FVIII, where 21 amino acids of the B-domain are left (before thrombin activation). Therefore, the CHMP considers that turoctocog alfa can be qualified as a new active substance.

Manufacture

Description of Manufacturing process and process controls

The routine manufacturing process is divided into three main steps including cell culture, capture and purification.

Turoctocog alfa is expressed in the Chinese Hamster Ovary (CHO) cell line, and exclusively non-animal-derived raw materials are used.

An overview for the manufacture of turoctocog alfa drug substance is provided in the flow-chart below.

Table 2: Flow diagram for the turoctocog alfa drug substance manufacturing process

Main section	Step	Description
Cell culture		**Vial from WCB**
	C1	Propagation in seed laboratory
	C2	Propagation in bioreactors
	C3	Cell culture in production bioreactor
	C4	Clarification of harvest
Capture	**Z1**	Capture by mixed mode chromatography, including detergent wash
Purification	**Z2**	Purification by immunoaffinity chromatography
	Z3	Purification by anion exchange chromatography
	K1	20 nm virus clearance filtration
	Z4	Purification and buffer exchange by size exclusion chromatography
		Drug substance (frozen)
Explanation: **C**: Steps in cell culture **Z**: Chromatographic step **K**: Filtration step		

Description of the cell culture and harvest process

The cell culture process comprises four steps including the propagation in the seed laboratory, propagation in bioreactors, and the main cell culture step in the production bioreactor.

In order to remove cells and cell debris, each harvest is clarified by a sequence of centrifugation and filtration before capture and purification is performed.

Process parameters with limits/ranges and the in-process controls are in place and described. Before the harvest, the viability is controlled and at the end of each cell culture, the in-process specification tests for sterility, mycoplasma and virus are performed.

Description of the capture and purification process

The capture process consists of a mixed-mode chromatography step. The purification process consists of immunoaffinity chromatography, anion exchange chromatography, virus reduction by nanofiltration (20 nm filter) and size exclusion chromatography.
Appropriate in-process controls comprised of process parameters and in-process tests are in place to control the different manufacturing steps.

Filling and storage

The drug substance obtained after the last chromatographic step is filled in containers and stored frozen, until transported to the formulation and filling department for the drug product.

Control of materials

Manufacture of turoctocog alfa

Development genetics and cell banking system:

The Applicant presented a sufficiently detailed description of the cloning procedure to generate the Research Cell Bank. The sources of the materials used are specified and selected literature regarding the human FVIII gene (for production of turoctocog alfa) is referenced.

The transgene plasmids were sequenced and characterized by restriction enzyme analysis. The cloning strategy for the turoctocog alfa expression vector is adequate and is described in sufficient detail.

The description and control of the expression construct is in accordance with the guideline ICH Q5B (Quality of Biotechnological Products: Analysis of the Expression Construct in Cell Lines Used for Production of r-DNA-Derived Protein Products).

A two-tiered cell-banking system is used, consisting of a MCB and a WCB which are both stored at two different locations. The documentation provided supports compliance with the guideline ICH Q5D (Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products).

Control of critical steps and intermediates

The control of the manufacturing process is based on the assessment of critical and non-critical process parameters during process development and evaluation. Appropriate in-process controls, composed of process parameters and in-process tests, were defined. A severity ranking for Critical Quality Attributes (CQA) for the manufacture of the drug substance was provided. The general approach to assure a consistent and reliable manufacturing process is in compliance with guideline ICH Q6B (Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products).

In-process controls are in place to control the fermentation process from the shake flask expansion to the bioreactor production The detection of contamination with virus, bacteria and mycoplasma when testing EPC results in discarding the batch.

The in-process controls are specified by limits and ranges and are considered appropriate. The in-process control limits assure a reproducible production process in the bioreactor over the cell production period.

In–process controls were also set for the clarification of the harvest by filtration and centrifugation as well as for the time from harvest to capture . In-process controls (process parameters and in-process

tests) were also defined for the capture and purification process. The hold times during the process steps were indicated and justified by validation data.

The virus inactivation step by detergent treatment is performed as part of the capture and purification process.

The virus reduction step is performed by nanofiltration using two 20 nm filters in series. The performance of this step is controlled by the in-process tests for leakage before and after filtration.

Process validation and/or evaluation

The process validation strategy of the turoctocog alfa drug substance manufacturing process is comprised of three important key elements including process design (process evaluation studies and validation of impurity reduction), Process Performance Qualification (PPQ) and continued process verification (extended monitoring of process performance) by compliance, yield and selected impurities; Critical Quality Attributes (CQA) for the manufacturing process were adequately defined.

The verification of the manufacturing process was done during Process Performance Qualification (PPQ). The Process Performance Qualification covers the three parts of the manufacturing process of the turoctocog alfa drug substance including cell culture, capture and purification. PPQ was performed with batches manufactured according to the commercial process and covering each step in order to demonstrate the consistency of the drug substance manufacturing process.

Process validation data were provided for all process steps covering the manufacture of turoctocog alfa. Overviews of process validation parameters, acceptance criteria and validation test results were provided as validation report summaries covering the process evaluation for the cell culture and harvest steps as well as for the capture and purification steps.
The process validation data provided is acceptable. Robust/consistent performance of the manufacturing process could be demonstrated. In general, the process validation for the manufacture of turoctocog alfa drug substance is considered acceptable.

Manufacturing process development
The process changes during development and their rationale are appropriately described. Between manufacturing campaigns, minor adjustments of the process as well as significant changes were introduced. The Applicant performed extensive comparability studies in compliance wihth the guideline ICH Q5E in order to investigate the impact of the process changes on product quality. In conclusion, comparability between nonclinical batches, clinical batches and PPQ batches was demonstrated. The process is therefore consistent and reproducible and yields drug substance of adequate quality.

Characterisation
Turoctocog alfa was extensively characterised by physicochemical methods in accordance with guideline ICH Q6B. The structural characterisation and the physicochemical properties confirmed the expected properties for a recombinant FVIII product.

The Applicant provided justification that turoctocog alfa is converted to the same FVIIIa as endogenous FVIII. Data on the biological in vitro characterisation including the kinetics of interaction with VWF and the characterisation of co-factor activity as well as rates for activation and inactivation were provided as part of the dossier.

The comparability of representative batches throughout development and commercial manufacture as well as with the primary reference materials for turoctocog alfa was demonstrated.

In general, the impurity profile regarding product- and process-related impurities was appropriately investigated. Selected impurities are included in the drug substance specification in order to ensure the quality of the drug substance and the final drug product.

Control of drug substance

Specification

The drug substance is appropriately controlled by the parameters tested including specifications for product- and process-related impurities. The release parameters and their specifications are adequate and meet the requirements as outlined in guideline ICH Q6B.

The specifications for drug substance mainly comprise the following parameters: Appearance, pH, identity, potency, specific activity, content, purity, product-related substances, product-related impurities, process-related impurities, peptide map, microbial count, and bacterial endotoxins.

The acceptance criteria for the control parameters are based on historical data including preclinical and clinical batches from process development as well as from performance qualification batches.

In general, the specifications are in accordance with Ph. Eur. requirements. The acceptance criteria assure that turoctocog alfa drug substance meets consistent quality.

Analytical procedures and validation of analytical procedures

The description of the analytical procedures and the provided validations are in general acceptable.

The development of the Host Cell protein assay (ELISA) was described in sufficient detail in order to evaluate the analysis data presented for HCP.

Batch analyses

Appropriate batch analyses data were provided.

Reference standards or materials

The potency standards PRM and SRM were calibrated against WHO 8th International Standard Factor VIII Concentrate (NIBSC code: 07/350) using the chromogenic assay (Ph. Eur. monograph 2.7.4). Both reference standards have undergone release testing and stability data were provided. The reference materials are sufficiently described and are acceptable.

Container closure system

The primary packaging materials for storage of the drug substance are in compliance with Ph. Eur. and are suitable for the intended use.

Stability

Turoctocog alfa drug substance will be stored frozen, the proposed shelf life is 24 months. The primary and supportive stability studies were performed according to the current ICHQ5C guideline. The parameters chosen to investigate the stability of the drug substance are acceptable.

Based on the currently available stability data for drug substance a maximum shelf life of 24 months appears justified.

Facilities and equipment

The information provided for the manufacture of turoctocog alfa drug substance regarding facilities and equipment is considered appropriate.

2.2.3. Finished Medicinal Product

Description and composition of the drug product

The composition of Novoeight is presented in the table below.

Name of components	Quantity (nominal) per vial of lyophilised powder[1]	Quantity per mL in the withdrawal volume	Function	Reference to standards
Active substance				
turoctocog alfa drug substance	250 IU	62.5 IU	Active ingredient	Novo Nordisk A/S
turoctocog alfa drug substance	500 IU	125 IU	Active ingredient	Novo Nordisk A/S
turoctocog alfa drug substance	1000 IU	250 IU	Active ingredient	Novo Nordisk A/S
turoctocog alfa drug substance	1500 IU	375 IU	Active ingredient	Novo Nordisk A/S
turoctocog alfa drug substance	2000 IU	500 IU	Active ingredient	Novo Nordisk A/S
turoctocog alfa drug substance	3000 IU	750 IU	Active ingredient	Novo Nordisk A/S
Excipients				
L-Histidine			Buffer	Ph Eur, USP, JP
Sucrose			Stabiliser	Ph Eur, USP, JP
Polysorbate 80			surfactant	Ph Eur, USP, JP
Sodium Chloride			Stabiliser	Ph Eur, USP, JP
L-Methionine			Antioxidant	Ph Eur, USP, JP
Calciumchloride dihydrate			Stabiliser	Ph Eur, USP, JP
Water for injections			Solvent	Ph Eur, USP, JP
Sodium hydroxide			pH adjustment to 6.9[2]	Ph Eur, USP, JP
Hydrochloric acid			pH adjustment to 6.9[2]	Ph Eur, USP, JP
Headspace gas				
Nitrogen			Headspace gas	Ph Eur, USP, JP

[1] Nominal quantity per vial refers to the quantity per 4 mL

[2] The pH of the formulated drug product is adjusted by adjusting the pH of the buffer solution used for dilution during preparation

The finished product is formulated with L-histidine, sucrose, polysorbate 80, sodium chloride, L-methionine, calcium chloride.

All excipients are of non-animal derived origin and of pharmacopoeial quality. They are common in lyophilized parenteral products and their function appears justified.

Turoctocog alfa drug product is filled into vials as a concentrated bulk solution and is to be reconstituted with 4.3 ml of solvent 0.9 % sodium chloride. A 0.3 ml overfill serves to assure a labelled 4 ml volume for administration. The product is for single-use and does not contain antimicrobial preservatives. The non-sterile bulk drug substance is sterile filtered, filled into vials and lyophilized in an aseptic process to assure sterility of the finished product.

The solvent 0.9% sodium chloride solution is presented in a prefilled 5 ml syringe. The solvent is made of sodium chloride and WFI which are both of Ph. Eur. quality. All components of the pre-filled syringe coming into contact with the product are of Ph. Eur. quality.

All six presentations of turoctocog alfa are filled into 5 ml vials of type I glass according Ph. Eur. Vials are closed with rubber stoppers which meet Ph. Eur. requirements. The composition of the product also contains a sterile, disposable vial adapter. Compatibility of the product with the primary packaging and the transfer device has been demonstrated. No administration set is provided with the product.

The drug product formulation is mainly based on the knowledge of FVIII stabilization from literature and from Novo Nordisk's experience with its own recombinant products.

Pharmaceutical Development

In general the pharmaceutical development of the drug product has been adequately described. The choice of excipients and the composition of the product appear justified and are comparable to other lyophilized recombinant coagulation factors for intravenous use.

The drug product formulation is mainly based on the knowledge of FVIII stabilization from literature and from Novo Nordisk's experience with its own recombinant products. During development the applied manufacturing process has been optimised. The minor differences between the manufacturing processes relate to the following changes:

- Optimization of the lyophilisation process
- Optimisation of the filling process

Manufacture of the product

The drug product manufacture is performed in equipment that is qualified for the intended purpose. All equipment coming into contact with the product is dedicated to turoctocog alfa drug product and is cleaned/ sanitized/depyrogenated in accordance with GMP requirements.

The manufacturing process has been described in sufficient detail. Maximum processing times, including hold times are specified.

Process Validation

Risk assessments have been performed to identify the steps in the manufacturing process with an impact on the critical quality attributes (CQA's), to eliminate unacceptable risks and define mitigating actions if moderate risks are identified. The lyophilisation process has been validated in compliance with the Note for guidance on process validation (CPMP/QWP/848/96). Selecting acceptance limits based on phase 3 batch specification, and setting tighter specifications for release can be accepted, provided batch analysis data on conformance lots demonstrates that after full scale validation the product meets those release specifications consistently. Challenging conditions are chosen during the validation demonstrating that the process is sufficiently robust.

Control of Drug Product

The release testing of turoctocog alfa drug product is performed by validated assays. These are mostly compendial analytical methods for which no validation is presented, because Ph. Eur. test methods are considered as validated methods. In the DS section the analytical methods are adequately described. The B-domain truncated rFVIII turoctocog alfa and the International Standard for Factor VIII concentrate behave similarly in the potency assays. This is demonstrated by data from the applicant, as well as by data obtained during the pre-authorisation testing at the control laboratory PEI (Paul Ehrlich Institute, Germany), both justifying calibration of turoctocog alfa drug product against the International Standard for factor VIII. The applicant has adequately investigated potential new impurities that might appear upon drug product manufacture or storage. The applicant has defined critical quality attributes as part of the control strategy. A severity rate has been defined to categorize the impact of a CQA on product quality or stability. The entire control strategy and selected specifications appear in accordance with the ICH Q6B, and the production process is well under control. Consistency of product quality is demonstrated by batch release data. Some specifications might be tightened, when more manufacturing experience and commercial batch release data are available.

Product specifications

The applicant followed recommendations as outlined in ICH Q6B for setting specifications. Specifications for drug product are based on pharmaceutical development data and manufacturing experience, including stability data. The specifications appear justified and some may be revised with manufacturing experience. Drug product specifications comprises the following:

Appearance, pH, identification, potency, purity, product-related impurities, content , particulate matter, osmolality, bacterial endotoxin, sterility.

In general, the specifications are in accordance with Ph. Eur. requirements.

Container closure system

The container/closure system is in compliance with Ph. Eur. requirements. A transfer device is part of the secondary packaging to allow for the transfer of the solvent into the drug product vial and for the transfer of the reconstituted product into the syringe. Compatibility of the container/closure with the product is demonstrated by data, including integrity tests.

Stability of the product

Stability studies have been performed in accordance with ICHQ5C at real time and at accelerated conditions. The applicant's proposal of a shelf life of 24 month at 5°C is acceptable, including up to 6

month at room temperature (≤30°C). Up to 6 month storage at room temperature (≤ 30°C) can be accepted, since the release and shelf life specifications have been set sufficiently tight, assuring a product of consistent quality and purity during the entire proposed shelf life.

Therefore, the stability data presented so far are considered useful to define a suitable drug product shelf life.

Drug Product (Solvent 0.9% sodium chloride solution)

The information provided for the solvent 0.9% sodium solution in a pre-filled syringe is considered satisfactory to demonstrate that the solvent is produced in a well-controlled, validated manufacturing process. Process and batch consistency is demonstrated. 24 month real time/real temperature stability data without any excursions are available at the moment. The proposed shelf life of 36 month at 5°C to 30 °C can be accepted.

Adventitious agents safety evaluation

TSE compliance
The active drug substance of turoctocog alfa is produced in genetically engineered Chinese hamster ovary (CHO) cells using serum-free medium. No material of animal origin is added during fermentation of turoctocog alfa. The MCB and WBC which have been established for the expression of turoctocog alfa are free from TSE-risk substances.

Virus safety
Turoctocog alfa is expressed using genetically engineered CHO cells. The fermentation process for turoctocog alfa is in serum-free medium. No other material of animal origin is added during fermentation of turoctocog alfa. This minimises possible contamination by adventitious viruses. The cells used for production of turoctocog alfa have been sufficiently screened for viruses. These tests failed to demonstrate the presence of any viral contaminant in the master cell bank or cells at the limit of in vitro cell age used for the expression of turoctocog alfa. The exception was the detection of intracellular A-type and C-type retroviral particles which are well known to be present in rodent cells. However, this is acceptable since there is sufficient capacity within the manufacturing procedure of turoctocog alfa for reduction of this type of virus particle therefore, there are no concerns regarding the production process of turoctocog alfa.

The purification process of turoctocog alfa includes several steps for inactivation/removal of enveloped viruses. The effectiveness of these steps has been sufficiently demonstrated.

In summary, the virus and TSE safety of turoctocog alfa has been sufficiently demonstrated.

Pre authorisation testing:
As discussed under the control of drug product section, the testing of the drug product prior to authorisation was requested and concluded the following:

The preauthorisation testing of turoctocog alfa DP lots has not indicated any deviation from established release specifications for potency, based on the chromogenic substrate assay.
All drug product samples, the controls and the reference materials showed similar behaviour in the parallel line and in the slope ratio model of evaluation. Hence, labelling of turocotocog alfa drug product relative to the FVIII International Standard in IU/ml seems adequate.

Both, the chromogenic substrate and the one stage clotting assay appear suitable for monitoring turoctocog alfa in clinical samples.

GMP status:
Valid GMP certificates were available for the facilities involved in the manufacture, storage and testing of the turoctocog drug substance and drug product or the generation and storage of the Master Cell Bank (MCB) and Working Cell Bank (WCB).

The manufacturing sites for drug substance and drug product have been inspected and accepted.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Turoctocog alfa is a B-domain-truncated recombinant rFVIII produced in CHO cells. After activation, turoctocog alfa is structurally and biochemically similar to plasma-derived FVIII. The rFVIII has been sufficiently characterised with respect to physicochemical and biochemical properties.

The production of the transgenic CHO cell line and the cell banking were performed in accordance with the relevant guidance documents. The upstream fermentation process and the downstream purification process were appropriately validated.

The drug substance manufacturing process is well controlled, leading to turoctocog alfa drug substance of consistent quality with an acceptable level of residual product- and process-related impurities. In addition, the risk for viral contamination is minimised through the sufficiently controlled cell banking system and fermentation process. During drug substance purification two effective virus reduction steps were incorporated.

The following issues regarding the turoctocog alfa drug substance were raised during the evaluation process and were sufficiently addressed by the applicant.

The development of the Host Cell Protein (HCP) assay was described in more detail in order to evaluate the analysis data presented for HCP.

In addition, the proposed shelf life of the drug substance of 24 months when stored frozen was supported by updated stability data for batches of the commercial process.

The B-domain truncated rFVIII turoctocog alfa and the International Standard for Factor VIII concentrate show similar behaviour in the potency assays, concluding that calibration against the International Standard for factor VIII is appropriate.

Suitability of the drug product with the container/closure system is demonstrated by respective studies and stability of the final product.

The proposed shelf life of 24 months at 2-8 °C with up to 6 months at ≤30°C is considered acceptable.

The CHMP agreed with the applicant's responses to the list of questions and all the questions raised during the procedure have now been adequately addressed.

No quality aspects impacting on the benefit risk balance have been identified for NovoEight.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the data presented indicate that turoctocog alfa drug product is manufactured in a validated, controlled process taking into consideration relevant guidance documents. Batch release data confirm a product of consistent quality. From a quality point of view turoctocog alfa is recommended for approval.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends points for further investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical safety evaluation programme of turoctocog alfa was designed in accordance with the guideline for biotechnology-derived pharmaceuticals provided by the International Conference of Harmonisation (ICH), ICH S6(R1), 2011 and the parts of ICH M3(R2), 2009 relevant to biopharmaceuticals, to support clinical use in males with congenital FVIII deficiency. *In vivo* studies were performed in mouse, rat, dog and monkey. All pivotal safety studies were conducted in accordance with current regulatory requirements and in compliance with the principles of Good Laboratory Practice (GLP). Nevertheless, the single dose escalation toxicity, one local tolerance study in Cynomolgus monkeys (as part of the single dose escalation study) and the immunogenicity study have not been performed in GLP-compliance.

2.3.2. Pharmacology

Primary pharmacodynamic studies

A number of *in vitro* studies were conducted with turoctocog alfa to determine the activity of turoctocog alfa in two different thrombin generation assays and to investigate the interaction of turoctocog alfa with von Willebrand Factor (vWF) and with monoclonal antibodies (mAbs). Additionally, the cofactor activity and the rates of activation and inactivation of turoctocog alfa were determined. The results are shown in Table 7.

Table 7: *In vitro* studies

Type of study	Test system or Species/ Strain	Method of Administration	Doses[a] (IU/kg)	Gender and No. per Group	Noteworthy Findings	GLP Compliance	Study Number
Species cross-reactivity	*In vitro system*	N/A	N/A	n/A	Turoctocog alfa enhanced thrombin generation in rat, cynomolgus monkey and human plasma in a dose-dependent manner. This demonstrates species cross-reactivity of turoctocog alfa to rat and cynomolgus	No	MKja070801
Thrombin generation assay	*In vitro* system, cell model	N/A	N/A	N/A	Dose dependent increase in thrombin generation. Similar thrombin generation capacity by turoctocog alfa and Advate®, ReFacto® and Haemate®.	No	MKja080602
vWF interaction	*In vitro* system – Biacore®	N/A	N/A	N/A	Turoctocog alfa and ReFacto® bind vWF with very similar affinities.	No	EgPe070901
vWF interaction	*In vitro* system - ELISA	N/A	N/A	N/A	Turoctocog alfa, Advate® and ReFacto® bind vWF with very similar affinities.	No	EgPe0805
SDS-PAGE and Western blot	*In vitro* system - Electro-phoresis	N/A	N/A	N/A	FVIII related peptides, detected by Western Blot using different FVIII antibodies, are similar for turoctocog alfa and different commercially available FVIII products.	No	MKja080601
Kinetics mAb by SPR	*In vitro* system – Bioacore®	N/A	N/A	N/A	Binding constants of different FVIII mAbs are similar for turoctocog alfa , Advate® and ReFacto®.	No	AGRU240608

The *in vivo* efficacy was documented and the dose-response relationship evaluated in two different studies (Study No. TEIm070501 and SAQ070601) in the haemophilia A mice (FVIII knock-out mice) model. The pharmacokinetics and pharmacodynamics of turoctocog alfa were also evaluated in haemophilia A dogs (Study No. MiE070601) and compared to another licensed FVIII product. The results are shown in Table 8.

Table 8: *In vivo* studies

Type of study	Test system or Species/ Strain	Method of Administration	Doses[a] (IU/kg)	Gender and No. per Group	Noteworthy Findings	GLP Compliance	Study Number
Tail bleeding in F8 knock-out mice	F8 knock-out mice and CB57BL mice	Via a catheter inserted in a. carotis	0, 1, 5, 20, 200 of turoctocog alfa and Advate®	Female and male: 8 animals pr each dose group	Bleeding time and blood loss were significantly longer in vehicle treated F8 knock-out mice compared to normal CB57. The bleeding time and blood loss after administration of 200 IU/kg Advate® or turoctocog alfa was not significantly different from normal controls. No difference in potency was observed between Advate® and turoctocog alfa.	No	TElm070501
Knee injury model in F8 knock-out mice	F8 knock-out mice	i.v. tail injection	200 of turoctocog alfa and Advate®	24 animals pr group. In total 72 mice.	F8 knock-out mice had a visual bleeding score (VBS) of 2.04 (SD1.30). Treatment with turoctocog alfa and Advate® significantly reduced the bleeding with a mean of 0.58 (SD 0.93) and 0.50 (SD 1.06) respectively. The mean change in joint diameter for F8 knock-out, untreated, and treated with turoctocog alfa and Advate® respectively was: 1.23 mm (SD 0.94); 0.32 mm (SD 0.39) and 0.25 mm (SD 0.39).	No	SAQ070601
PK/PD study in haemophilia A dogs	Haemophilia A dogs	i.v. injection	100 of turoctocog alfa and Advate®	2 animals. Each dog received both turoctocog alfa and Advate® in a cross-over study design	Turoctocog alfa and Advate® were equally capable of normalising whole blood clotting time and showed similar activity profile over time.	No	MiE070601

a - Single dose unless specified otherwise.

Secondary pharmacodynamic studies

Secondary pharmacodynamic studies have not been submitted.

Safety pharmacology programme

Core endpoints of safety pharmacology testing (central nervous system, cardiovascular system, and respiratory system) have been addressed in the toxicology programme in Cynomolgus monkeys. In the single dose toxicity study potential effects on cardiac effects and blood pressure were investigated. The repeated dose toxicity study integrated the following parameters: blood pressure, electrocardiography, respiratory rate, neurological/CNS endpoints and urinalysis.

No adverse effects on food consumption, behaviour or body temperature were observed.

In the repeat dose toxicity study in the primate a statistical significance ($p<0.05$) with regard to mean systolic pressure was evident in week 2. However, this was attributed to decreased levels in the controls. Values in the dose groups at week 2 were within the range of values recorded pre-treatment.

There was no consistent pattern in the data to indicate an effect of treatment on heart rate, ECG intervals or waveform, respiratory rate or depth.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were submitted.

2.3.3. Pharmacokinetics

The pharmacokinetics and toxicokinetics of turoctocog alfa were investigated in FVIII knock-out mice, Sprague Dawley rats, haemophilia A dogs, and Cynomolgus monkeys. Various bioassays have been developed to assess turoctocog alfa pharmacokinetics. In the PK studies, plasma samples were analysed for FVIIII coagulant activity (FVIII:C) by a two-stage chromogenic assay (COA) while antigen (ag) concentration was determined by an Enzyme Linked Immuno Sorbent Assay (ELISA). For the pivotal toxicokinetics in rats and monkeys, a chromogenic assay was validated and used. Anti-turoctocog alfa and anti-turoctocog alfa neutralising antibody assays were validated for the pivotal toxicity studies in rats and monkeys. Pharmacokinetics of turoctocog alfa was compared to those of other recombinant FVIII products, ReFacto and Advate.

Table 9: Summary of pharmacokinetic and toxicokinetic studies of turoctocog alfa

Type of study	Species	Administration	Study No.
PK of turoctocog alfa, Advate and ReFacto administered i.v. to FVIII KO mice	mice	single iv injection	DKPF070802
PK and PD study of turoctocog alfa and Advate in haemophilia A dogs	dog	single iv injection	MiE070601
Toxicokinetics	monkey rat monkey	single iv injection multiple iv injection multiple iv injection	207402 211030 208012
A quantitative whole body autoradiography study on C57Bl/6 and vWF KO mice after a single dose of turoctocog alfa (distribution)	mouse	single iv injection	208356

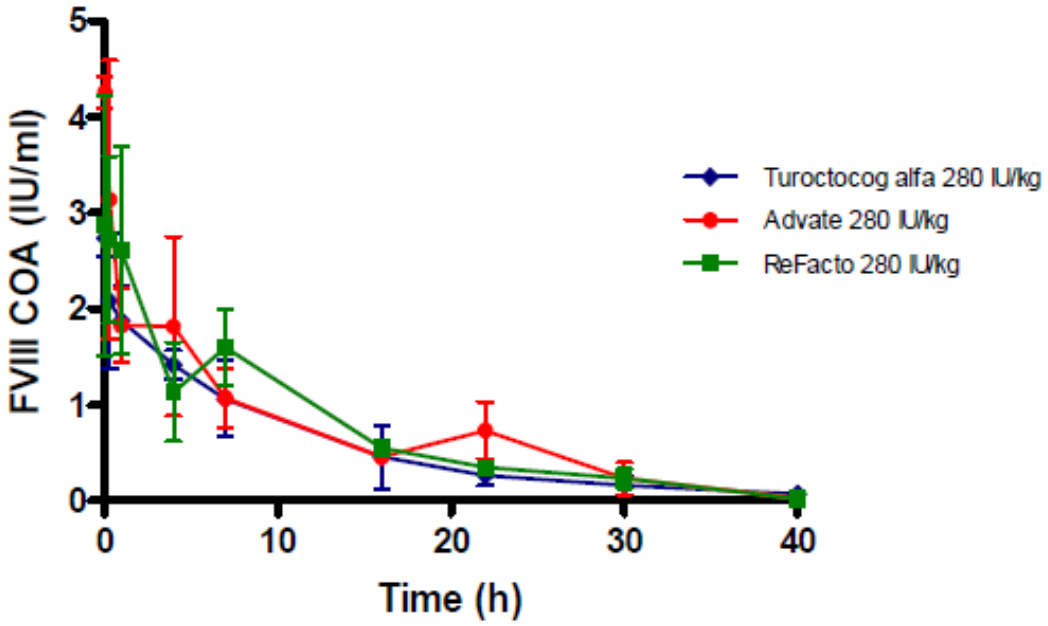
Absorption of turoctocog alfa was evaluated following intravenous administration, which is the intended clinical route of administration. Pharmacokinetic assessments comprised FVIII activity, initial plasma concentration (C0.25h), maximum observed concentration (Cmax), terminal half-life (t1/2), area under concentration versus time curve (AUC), AUC from zero to 24 hours (AUC0-24h), total body clearance (CL), volume of distribution after a single dose (Vz), volume of distribution at steady state (Vss).

Non-compartmental analysis (NCA) was performed in male FVIII knock-out mice, haemophilia A dogs, Cynomolgus monkeys and in male and female Sprague Dawley rats.

In study DKPF070802, the pharmacokinetics of various doses (8, 80, 180 or 280 IU/kg) of turoctocog alfa was determined following intravenous administration in 68 FVIII knock-out mice and compared to

that of 280 IU/kg doses of two marketed FVIII products, Advate and ReFacto. Dose proportionality was found in the range of 80-280 IU/kg. Regarding the calculated PK parameters as obtained by NCA no major differences were observed in the half-lives (6.7-7.8h, chromogenic activity), clearances (10-11 ml/h/kg, chromogenic activity) or volume of distributions (97-117 ml/kg, chromogenic activity) between turocotog alfa, ReFacto or Advate.

Figure 2: Pharmacokinetics of FVIII in FVIII knock-out mice. FVIII activity as function of time after i.v. administration of 280 IU/kg turoctocog alfa, ReFacto and Advate



The PK/PD profile of turoctocog alfa was evaluated in haemophilia A dogs and compared to Advate (Study No. MiE070601). Pharmacokinetic analysis was carried out by non-compartmental analysis (NCA) of FVIII plasma activity (chromogenic assay). From the data the following parameters were estimated: C_{max}, AUC_{0-t}, $T_{1/2}$, $AUC_{0->\infty}$, CL, MRT, and V_{ss}. In addition two PK parameters used in the haemophilia field were calculated: the incremental recovery (K-value) and *in vivo* recovery (IVR). The pharmacokinetics of FVIII was determined following a single intravenous administration of 100 IU/kg turoctocog alfa and Advate in a cross-over design. FVIII was assayed in plasma samples by FVIII chromogenic and clot activity assays. The terminal $t_{½}$ for turoctocog alfa was in the range of 7.2–10.5 hours. The PK parameters for turoctocog alfa and Advate were similar, but the two dogs had a different response towards the FVIII products, probably due to the presence of antibodies in dog K01. Nevertheless, the PK parameters for turoctocog alfa and Advate were similar within each individual dog and the obtained data are in agreement with published studies of FVIII compounds in haemophilia A dog.

A quantitative whole body distribution study was performed in male C57Bl/6 and in male vWF KO mice with 125I-turoctocog alfa (Study No. 208356). The 125-iodine label was unspecific in the tyrosine amino acids of turoctocog alfa. Animals were dosed with 0.028 mg/kg of radiolabelled turoctocog alfa,

corresponding to 295 IU/kg at 52µCi/kg. After a single dose of 125I- turoctocog alfa to C57Bl/6 mice a high amount of radioactivity was present in the liver and organs with high blood flow such as the kidney, lung and spleen. The corresponding tissue:blood ratios were 0.43 for liver, 0.48 and 0.26 for kidney medulla and kidney cortex respectively, 0.58 for lung and 0.39 for spleen.

No metabolism or excretion studies have been submitted.

No pharmacokinetic drug interaction studies have been submitted.

2.3.4. Toxicology

The toxicology program included single dose and repeat dose toxicity studies using rats and Cynomolgus monkeys as well as the evaluation of the local tolerance in New Zealand White rabbits, rats and male Cynomolgus monkeys. Additionally one immunogenicity study was performed in the rat. According to the applicant, most of the toxicity studies were conducted in compliance with GLP regulations, except the single dose escalation toxicity, one local tolerance study in Cynomolgus monkeys (as part of the single dose escalation study) and the immunogenicity study.

Single dose toxicity

In a non-GLP study, single dose toxicity was studied following a single intravenous administration at each dose level to male Cynomolgus monkeys. There were no decedents in the study and no clinical signs related to treatment were observed. In the absence of adverse local or systemic reactions to treatment, the single dose NOAEL was considered to be 5000 IU/kg.

Repeat dose toxicity

Repeat dose toxicity studies were performed in Sprague Dawley rats and Cynomolgus monkeys for up to 2 weeks duration with daily intravenous dosing up to 1250 IU/kg in the rat and 5000 IU/kg in the monkey. These studies were performed in compliance with GLP.

In the rat studies, toxicokinetics and immunogenicity were evaluated and in the monkey studies toxicokinetics and safety pharmacology were investigated.

In the rat study (study 211030) no decedents were observed. There were no toxicologically significant effects on clinical signs, body weights, food consumption, ophthalmoscopy, haematology, clinical chemistry, urinalysis, organ weights, and macroscopic or microscopic observations. Consistent with the species-foreign nature of human turoctocog alfa in rats, an antibody-specific immune response was generated in almost all treated animals along with a steadily reduced exposure from day 8 and until the end of dosing. Significant prolongation of mean APTT was seen in the recovery period in animals previously given 1250 U/kg/day. This effect was not considered to be adverse as there were no correlating clinical or histopathological findings. The non-immunogenic NOAEL was identified to be 1250 IU/kg/day.

In the monkey study (study 208012), turoctocog alfa was administered daily intravenously to male Cynomolgus monkeys for 14 days with dose levels of 50, 1000 and 5000 IU/kg/day. No treatment-related findings regarding safety pharmacology endpoints e.g. no effects on respiratory rate or depth, no effect on behavioural, autonomic or neurological measurements and no effect of treatment

on heart rate, ECG intervals or waveform were observed. Consistent with the species-foreign nature of human FVIII in cynomolgus monkeys, antibodies developed in 22 out of 24 dosed animals. 18 of the 22 monkeys had neutralising antibodies. As a result, APTT times increased in all animals with neutralising antibodies from day 10 to 14 (except in the animals dosed with 50 IU/kg/day where only one animal had an increase in APTT) and the effect was further pronounced in the recovery period.

APTT values were markedly prolonged on Day 14 in animals dosed with 1000 and 5000 IU/kg/day. In animals dosed with 50 IU/kg/day, there was also an increase in APTT at Day 14 except for in two animals without neutralising antibodies. There were no findings related to other adverse effects of turoctocog alfa in any of the animals and all findings in this study are considered to be related to the development of cross-reacting neutralising antibodies, resulting in acquired haemophilia.

Based on the findings a NOAEL for immunogenicity-related effects (antibody formation to a species-foreign protein) could not be determined. The NOAEL for non-immunogenicity related toxicity was 5000 IU/kg/day.

Genotoxicity

No genotoxicity studies have been submitted.

Carcinogenicity

Nonclinical carcinogenicity studies have not been submitted.

Reproduction Toxicity

Reproductive and developmental toxicity studies have not been performed with turoctocog alfa. Fertility was assessed by histopathology or reproductive organs in the repeat dose toxicity study using sexually mature male and female rats. No effects on the reproductive organs were seen.

Toxicokinetic data

The toxicokinetics of turoctocog alfa following a single intravenous administration of 50, 250, 500, 1250, 2500 or 5000 IU/kg were determined in male Cynomolgus monkeys with two animals per dose level (Study No. 207402). Systemic exposure to turoctocog alfa was confirmed in all animals with the exception of one animal given 50 IU/kg, due to high pre-dose plasma FVIII activity. Turoctocog alfa was assayed in plasma samples by a FVIII chromogenic activity assay. The individual t½, estimated for animals dosed with 250, 1250, 2500 and 5000 IU/kg, was in the range of 6.4 to 12 hours over the dose range. Estimated mean CL values of 0.00575 and 0.00755 (l/h/kg) were found following doses of 2500 and 5000 IU/kg, respectively. Both the C0.25h and AUC0-24h values increased with dose. The increase in exposure was proportional to dose based on C0.25h and less than proportional to dose based on AUC0-24h.

The toxicokinetics of turoctocog alfa after repeated dosing was evaluated in male and female Sprague Dawley rats, following i.v. administration once-daily for 14 consecutive days at dose levels 50, 250 or 1250 IU/kg (Study No. 211030). Blood samples for toxicokinetics were taken from animals on day 1, day 8 and day 14, with a further exposure sample on Day 5. Endogenous FVIII activity was high in

control animals, with AUC0-24h ranging from 30.2 to 43.8*IU/ml and Cmax ranging from 1.54 to 1.97 IU/ml. The terminal half-life (t1/2) could only be estimated for two composite profiles on day 1 at dose level 250 IU/kg and was 4.4 hours in males and 4.7 hours in females. For animals dosed i.v. on day 1 with 50, 250 or 1250 IU/kg, exposure to turoctocog alfa could generally be demonstrated above endogenous activity up to approximately 2 to 6 hours after dosing. Repeated administration once daily for 14 consecutive days at different dose levels, resulted in exposure to turoctocog alfa generally decreasing in both males and females due to antibodies formation.

The toxicokinetics of turoctocog alfa was evaluated in male Cynomolgus monkeys, following daily intravenous administration for 14 days at dose levels of 50, 1000 and 5000 IU/kg (Study No. 208012). The reversibility and/or delayed onset of any effects at the selected dose levels, over a 6-day recovery period, were also assessed. Systemic exposure increased approximately proportionally to the increase in dose based on C0.25h but less than proportionally based on AUC0-24h. The t½ estimated for animals dosed with 1000 and 5000 IU/kg on Day 1, was in the range of 5 to 12 hours. The lack of exposure at day 14 in the monkey following repeated dosing corresponded with the presence of neutralising antibodies. The antibodies were cross-reactive to endogenous FVIII in Cynomolgus monkeys.

Local Tolerance

In Study No.211272, the local tolerance of turoctocog alfa at the injection sites four days after a single perivenous, intravenous and intraarterial injection of turoctocog alfa was assessed in the ears of rabbits. A single dose of 0.15 ml (corresponding to approximately 20 IU/kg) per animal of turoctocog alfa administered either perivenously, intravenously or intraarterially in the ears of rabbits did not result in any signs of treatment-related systemic toxicity or treatment-related local clinical reactions. The injections caused very mild histopathological changes at the injection sites, characterised by inflammatory changes or haemorrhage. All changes reported at the turoctocog alfa treated sites were either comparable or had lower incidence and severity compared to the placebo-treated injection sites.

The local tolerance of turoctocog alfa was further assessed as an integrated part of the single and repeat dose toxicology studies in monkeys and the repeat dose toxicology study in rats (Study No. 207402, 211030 and 208012). In all these studies there was no evidence of local systemic toxicity.

Other toxicity studies

The non-GLP Study No.210401 aimed to investigate if daily intravenous dosing of turoctocog alfa to Sprague Dawley rats led to generation of anti-drug antibodies affecting exposure. Generation of antibodies was investigated after 2 and 4 weeks of dosing to evaluate the development of antibodies and to recommend an optimal duration of dosing in subsequent studies. Animals were treated with a daily intravenous (bolus) dose of 1250 IU/kg turoctocog alfa for 14 or 28 days.

No adverse clinical signs or injection site reactions were observed throughout the study. Analysis for anti-turoctocog alfa antibodies was made pre-dose, Day 16 and Day 30. All pre-dose samples were antibody negative and all samples from dosed animals were antibody positive. Antibodies against turoctocog alfa were present in all animals at Day 16 and 30. The titre increased from Day 16 to Day 30 indicating that the level of anti-turoctocog alfa antibodies increased over time. Together with a decreased FVIII activity within the first two weeks of dosing, two weeks dose duration was selected for the pivotal repeat dose toxicity study.

The content of product-related impurities at release and at end of shelf life in non-clinical batches was within the specification limits. Based on the higher dose levels (100-fold to clinical dose for bleeding prevention, and 25-fold to maximum dose on demand) administered in the non-clinical studies in Cynomolgus monkeys at NOAEL, these impurities are considered adequately qualified compared to maximum exposure of impurities at the recommended clinical dose at end-of-shelf-life- specification.No safety concerns have been raised.

2.3.5. Ecotoxicity / environmental risk assessment

Turoctocog alfa is a recombinant human coagulation factor VIII and once activated by thrombin cleavage the resulting rFVIIIa has the same structure as endogenous FVIIIa. According to the European Medicines Agency Guideline “Guideline on the environmental risk assessment of medicinal products for human use”, an environmental risk assessment is not required for proteins.

2.3.6. Discussion on non-clinical aspects

Pharmacodynamic effects of turoctocog alfa could be demonstrated in several *in vitro* studies. These studies demonstrated a dose dependent increase in thrombin generation, similar for turocotcog alfa and other licensed FVIII products. All products compared bind VWF with very similar affinities.

The *in vivo* studies were performed in the FVIII knock-out mouse (mouse haemophilia A model) and in haemophilia A dogs. In these studies, it was demonstrated that the effect of turoctocog alfa (200 IU/kg) was comparable to another licensed recombinant FVII product supporting the potential use of turoctocog alfa as replacement therapy in human haemophilia A patients. In the limited cross-over study in haemophilia A dogs, turocotcog alfa demonstrated a similar PK and PD profile as a comparator. In summary, turoctocog alfa is capable of normalising whole blood clotting time and showed similar activity profile over time as a licensed recombinant FVIII product. No secondary pharmacodynamic effects are expected and thus secondary pharmacodynamic studies were not submitted.

In accordance with the ICH S6 guideline, safety pharmacology aspects have been integrated into the toxicology programme. No adverse effects regarding safety pharmacology were observed.

Pharmacokinetic parameters of turoctocog alfa were investigated in FVIII knock-out mice, Sprague Dawley rats, haemophilia A dogs, and Cynomolgus monkeys after single and repeated intravenous administration. The pharmacokinetics for turoctocog alfa and the licensed recombinant FVIII products in FVIII knock-out mice was comparable and no major differences were seen in the calculated PK parameters (t½, CL or volume of distribution).

The PK parameters obtained in two haemophilia A dogs are in agreement with published data for FVIII in both haemophilia A patients and haemophilia A dogs.

Due to the high endogenous FVIII activity in the rat, sufficient data could not be generated to be able to draw conclusions regarding dose linearity. Both in rats and monkeys, a decrease in exposure was observed after repeated dosing, likely due to formation of cross reacting and neutralising antibodies to endogenous FVIII.

In a quantitative whole distribution study in male C56Bl/6 mice a high amount of radioactivity could be detected in the liver and organs with high blood flow such as the kidney, lung and spleen after a single dose of ^{125}I- turoctocog alfa.

Overall, the results of the PK studies in mice, rats, dogs and monkeys demonstrated that turoctocog alfa has the expected bioavailability and pharmacokinetic properties in comparison to the licensed recombinant FVIII products.

The toxicology programme for marketing authorisation application of turoctocog alfa included one single dose and two repeat dose toxicity studies using rats and Cynomolgus monkeys, as well as the evaluation of the local tolerance in New Zealand White rabbits, male Cynomolgus monkeys and rats as part of the single dose and the repeated dose study.

In the single dose monkey study, no findings related to treatment were observed and a NOAEL of 5000 IU/kg was determined.

During the administration of turoctocog alfa in the 2-week repeated dose study in monkeys, animals in all turoctocog alfa dose groups developed cross-reacting neutralising antibodies resulting in clinical and pathological signs of acquired haemophilia. However, there were no signs of adverse effects related to turoctocog alfa. In the 2 week repeat dose toxicity study in rats, an antibody-specific immune response was generated in almost all treated animals. The findings in this study are considered not to be directly related to turoctocog alfa but are indirect effects due to immunogenicity of this human protein in rats. Immunogenicity in rats towards a human FVIII is not considered predictive for the clinical situation. Based on these observations, it was concluded that turoctocog alfa toxicity studies of longer duration than 2 weeks would not provide additional relevant information or contribute to the safety evaluation to human use.

In the Cynomolgus monkey, single intravenous administrations of turoctocog alfa at six discrete dose levels, ranging from 50 to 5000 IU/kg were all well tolerated. In the rat model intravenous administration of turoctocog alfa to Crl:CD(SD) rats at 50, 250 or 1250 U/kg/day was well-tolerated. The NOAEL for immunogenicity-related effects (antibody formation to a species-foreign protein) could not be determined in the monkey study. The NOAEL for non-immunogenic related toxicity in the monkey was 5000 IU/kg/day and 1250 IU/kg/day in the rat, i.e. the highest doses tested. These findings are in accordance with findings in preclinical studies with other commercially available FVIII products.

All excipients and impurities found in the turoctocog alfa drug product are considered adequately non-clinical qualified for clinical use at end-of-shelf-life-specification.

The local tolerance of turoctocog alfa was evaluated by peri- and intravenous as well as intraarterial administration to New Zealand White Rabbits. A single dose of 0.15 ml (corresponding to approximately 20 IU/kg) per animal of turoctocog alfa administered in the ears of rabbits did not result in any signs of treatment-related systemic toxicity or treatment-related local clinical reactions. The injections caused very mild histopathological changes at the injection sites, characterised by inflammatory changes or haemorrhage. All changes reported at the turoctocog alfa treated sites were either comparable or had lower incidence and severity compared to the placebo-treated injection sites.

According to ICH S6 guideline recommendations, the omission of studies on genotoxicity, carcinogenicity and reproductive and developmental toxicity is justified.

2.3.7. Conclusion on the non-clinical aspects

In general, the data from the pharmacology and pharmacokinetic studies were considered sufficient to support marketing authorisation of turoctocog alfa. The non-clinical data are considered appropriate for the marketing authorisation application of turoctocog alfa as recombinant blood coagulation factor VIII. The results of the PK studies in mice, rats, dogs and monkeys treated with turoctocog alfa showed comparable bioavailability and pharmacokinetic properties to other licensed FVIII products. The immunogenicity findings in the single and multiple dose toxicity studies in rats and monkeys pose no concern as the immune reaction to turoctocog alfa was expected. Furthermore, the results of the toxicity studies showed no unexpected results with turoctocog alfa treatment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Trial ID	Phase	Doses	Number of dosed patients	Trial status	Trial description
Previously treated patients					
NN7008-3522	1	50 IU/kg (single dose) Advate: 50 IU/kg (single dose)	23 adolescent or adult patients with severe haemophilia A	Completed	*First human dose trial* A multicentre, multinational, open-label, first human dose, pharmacokinetic, safety, single-dose trial using a sequential design in patients with haemophilia A.
NN7008-3893	1	50 IU/kg (single dose)[a]	4 adult patients with severe haemophilia A	Completed	*Pharmacokinetic trial (two lots)* A multicentre, open-label, trial investigating the pharmacokinetics of a single dose of turoctocog alfa in patients with haemophilia A.
NN7008-3600	1	50 IU/kg (single dose)[a]	7 adult patients with severe haemophilia A *Pharmacokinetics:* 6 patients	Completed	*Pharmacokinetics in Japanese patients* A multicentre, open-label, singledose trial investigating the pharmacokinetics of turoctocog alfa in Japanese patients with haemophilia A.
NN7008-4015	1	50 IU/kg (single dose)	15 patients with severe haemophilia A (FVIII<1%)	Completed	*Pharmacokinetic trial* A multicentre, open-label trial investigating the pharmacokinetics of turoctocog alfa in patients with haemophilia A

NN7008-3543	3	*Prevention:* 20–40 IU/kg every second day or 20–50 IU/kg three times weekly. *Treatment of bleeds and surgery:* At the Investigator`s discretion. *Pharmacokinetics:* 50 IU/kg (single dose) preceded by preventive dosing for 3−6 months (wash-out period of ≥4 days prior to the pharmacokinetic session).	*Total (including subtrial)*: 150 adolescent or adult patients with severe haemophilia A. *Surgery sub-trial*: 9 patients *Pharmacokinetics:* 22 patients (same patients as in Trial NN7008-3522)	Completed	*Pivotal trial* A multicentre, multinational, openlabel, safety, efficacy, single-arm trial in patients with severe haemophilia A investigating turoctocog alfa when used for prevention and treatment of bleeds. The trial included a sub-trial designed to evaluate the safety and efficacy of turoctocog alfa when used for prevention and treatment of bleeding during surgical procedures and in the surgery period. The pharmacokinetics of turoctocog alfa was assessed following 3−6 months of preventive dosing in patients who had completed Trial NN7008-3522
NN7008-3545	3	*Pharmacokinetics*: 50 IU/kg (single dose). Patients' previous product: 50 IU/kg (single dose) *Prevention:* 25–50 IU/kg every second day or 25–60 IU/kg three times weekly. *Treatment of bleeds and surgery*: At the investigator's discretion.	*Total:* 63 paediatric patients (below 12 years of age) with severe haemophilia A. *Pharmacokinetics*: 28 patients	Completed	*Paediatric trial* A multicentre, open-label, non-controlled safety, efficacy and pharmacokinetic trial of turoctocog alfa in paediatric patients with haemophilia A.
NN7008-3568	3	*Prevention:* 20–50 IU/kg every second day or 20–60 IU/kg three times weekly. *Treatment of bleeds/on- demand and surgery:* At the investigator's discretion.	*Total (including sub-trial):* 187 paediatric, adolescent or adult patients with severe haemophilia A[b] *Surgery sub-trial*: 2 patients	Ongoing	*Extension trial* A multicentre, multinational, open- label, non-randomised, single-arm, safety and efficacy extension trial in patients with haemophilia A investigating turoctocog alfa when used in a preventative or on-demand treatment regimen. The trial includes a sub-trial designed to evaluatesafety and efficacy of turoctocog alfa during surgery.
NN7008-3553	4	Patients will be treated with commercially available turoctocog alfa as prescribed by the treating physician in clinical daily practice.	None	Planned	*Non-interventional study* A multicentre non-interventional study of safety and efficacy of turoctocog alfa during long-term treatment of severe haemophilia A.

Previously untreated patients					
NN7008-3809	3	*Prevention:* 15–50 IU/kg once weekly or 20–50 IU/kg every second day or 20–60 IU/kg three times weekly. *Treatment of bleeds and surgery:* At the investigator's discretion.	None[c]	Ongoing	*Trial in previously untreated patients* Safety and efficacy of turoctocog alfa in prevention and treatment of bleeds in paediatric previously untreated patients with haemophilia A.

[a] Trials 3600 and 3893: single-dose pharmacokinetic assessment was preceded by preventive dosing [b] according to the dosing regimen in Trial 3543 (wash-out period of ≥4 days prior to the pharmacokinetic session). [b] Until the cut-off date of 21 November 2011. [c] No patients were dosed in Trial 3809. IU: international units.

2.4.2. Pharmacokinetics

Analytical methods

The FVIII activity of turoctocog alfa was determined using both the one-stage activated partial thromboplastin time (aPTT) assay (clotting assay) and a two-stage chromogenic substrate assay (chromogenic assay) in the clinical trials assessing the pharmacokinetic profile of turoctocog alfa. Detection of FVIII inhibitors was performed using the Nijmegen modified Bethesda assay. A cut-off point for clinical relevant levels of inhibitors was set to ≥ 0.6 BU which corresponds to 66% remaining FVIII activity according to guideline recommendations.

An international, multi-centre, randomised and blinded field study was designed to evaluate and compare assay performance of turoctocog alfa (2000 IU/mL vial, batch no. VR40187 [Lot C]) and Advate in spiked plasma (to reach levels of 0.03, 0.2, 0.6 and 0.9 IU/mL) from patients with haemophilia A at different clinical laboratories with the methodology and reagents routinely used in the laboratories. The result of the chromogenic/one-stage clotting assay is presented below.

Table 10: Chromogenic/One-stage clotting assay result ratio – Field study

	Advate				turoctocog alfa				Standard:
IU/mL	0.03	0.2	0.6	0.9	0.03	0.2	0.6	0.9	0.8
Ratio	0.66	0.90	1.12	1.19	0.68	1.01	1.23	1.30	0.99

Scientific and Standardisation Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH)

Comparable and consistent estimates of target value were observed for turoctocog alfa and Advate.

Pharmacokinetics data in the target population

A total of 61 patients with haemophilia A have participated in trials which included full pharmacokinetic assessment of turoctocog alfa. As 22 of these patients had pharmacokinetic profiles determined in both Trial 3522 and Trial 3543, the total number of pharmacokinetic assessments of turoctocog alfa was 83.

The age range of enrolled patients was 1−54 years. There were only two adolescent patients (12−<18 years) included in the trials. A total of 28 patients were children (<12 years). All patients were previously treated patients with ≥ 150 exposure days (patients ≥ 12 years) or ≥ 50 exposure days (patients <12 years) to any FVIII product.

The pharmacokinetics of turoctocog alfa was investigated in four clinical pharmacology trials in patients with haemophilia A (studies NN77008-3522, NN7008-3893, NN77008-3600, NN7008-4015). In addition, a phase 3 trial (NN7008-3543) contributed to the assessment, where the pharmacokinetics of turoctocog alfa was assessed following 3−6 months of preventive dosing in patients who had completed Trial NN7008-3522.

The pharmacokinetic parameters of turoctocog alfa were based on FVIII activity (FVIII:C) measurements.

Pharmacokinetics in adult and adolescent patients

Study NN7008-3522: In this first human dose trial, the pharmacokinetics of turoctocog alfa was compared to the pharmacokinetics of Advate in patients with haemophilia A. Analyses were performed on three analysis sets in this trial: unadjusted data, data adjusted for actual dose and strength (dose-adjusted) and dose-adjusted data excluding outliers.

Three patients have been excluded from analysis since these deviations may potentially affect the pharmacokinetic evaluations: In two patients, turoctocog alfa plasma profiles were not indicative of a normal i.v. short infusion administration and one patient had one outlying value in the turoctocog alfa plasma profile 30 min post-dosing. In addition, one patient had a pre-turoctocog alfa FVIII activity of 0.105 IU/mL. Furthermore, the $t_{½}$ from one patient has been excluded as it was considered an outlying value (48.5 hours).

The pharmacokinetics of turoctocog alfa after single-dose administration i.v. to adult and adolescent previously treated patients with haemophilia A was investigated in a total of 23 patients above 12 years of age (mean age: 24 years; range: 13− 54 years). A total of 20 patients were included in the full analysis set, adjusted for dose and excluding outliers:

Table 11: Single-dose pharmacokinetics of turoctocog alfa in adult and adolescent patients with haemophilia A (Trial NN7008-3522) – Full analysis set, dose-adjusted and excluding outliers

Trial NN70083522	**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)	14.22 (3.75)	18.70 (5.08)
Total CL (mL/h)	274.9 (87.77)	209.7 (67.15)
Weight normalized CL (mL/h/kg)	3.74 (0.95)	2.87 (0.80)
t½ (h)	10.83 (4.95)	10.04 (3.59)[a]
Vss (mL/kg)	53.43 (10.88)	44.31 (28.17)
Cmax (IU/mL)	1.07 (0.16)	1.54 (0.29)
MRT (h)	15.43 (6.36)	16.40 (10.14)

Dose: 50 IU/kg turoctocog alfa (single i.v. dose); N=20
[a] NOTE: t½ (chromogenic assay) differ from the result presented in the CTR due to exclusion of an outlier;

After the end of the turoctocog alfa infusion, the FVIII activity level declined in an exponential way with a tendency to a slight biexponential decay pattern. In 17 out of 23 patients the FVIII activity was measurable for up to 48 hours post-dosing of turoctocog alfa. The mean residual activity levels at 48 hours post-dosing was 0.03 IU/mL, ranging from 0.0125 IU/mL (LLoQ) to 0.13 IU/mL. The remaining 6 patients had FVIII values below the LLoQ at 48 hours post-dosing. The mean Vss of turoctocog alfa indicated limited distribution into the extravascular space.

Study NN7008-3543: Part A (PK session) of this pivotal phase 3 trial investigated PK following preventive dosing in patients who completed Trial NN7008-3522. The pharmacokinetic profile after the first injection of turoctocog alfa, obtained in Trial NN7008-3522, were compared to the results obtained after 3– 6 months of preventive dosing with turoctocog alfa in Trial NN7008-3543.

A total of 22 patients participated in the pharmacokinetic part of Trial NN7008-3543. As data from 3 patients were excluded from Trial NN7008-3522 and data from 4 patients were excluded from Trial NN7008-3543, the compare analysis set comprised 15 patients. The patients received 36– 65 doses of turoctocog alfa prior to the pharmacokinetic session in Trial NN7008-3543.

The mean FVIII activity at each of the specific time points in the interval 15 min to 4 hours post-dosing (i.e., at time points 15 min., 30 min. and 1 hour) was slightly higher in Trial NN7008-3543 (after preventive dosing for 3– 6 months) compared to Trial NN7008-3522 (first dose of turoctocog alfa). This difference was mainly noted for the clotting assay.

The individual pharmacokinetic profiles showed that no patients had lower FVIII activity following 3– 6 months of preventive dosing (Trial NN7008-3543) compared to the first dosing with turoctocog alfa (Trial NN7008-3522). This was also the case when examining the full analysis set including outliers.

Table 12: Comparison of pharmacokinetic endpoints of turoctocog alfa after first dose administration (Trial NN7008-3522) and after preventive dosing for 3–6 months (Trial NN7008-3543) to adult and adolescent patients with haemophilia A – Compare analysis set, dose-adjusted

	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)
t½ (h)	10.47 (2.34)	10.50 (5.19)	9.47 (2.38)[a]	8.65 (2.09)
Vss (mL) (total)	3576.7 (589.8)	3412.4 (702.9)	2814.8 (883.9)	2806.6 (783.6)
Cmax (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
[a]NOTE: t½ (chromogenic assay) differ from the result presented in the CTR due to exclusion of an outlier; for details, please refer to Section 3.1.1, outliers.

Pharmacokinetics in children

Study NN7008-3545: The pharmacokinetics of a single dose of turoctocog alfa in children (0– <12 years) with haemophilia A was investigated in this open-label, non-controlled trial. The mean age of the young 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). Sampling time points were at pre-dose and at 30 min., 1, 4, 10, 24 and 48 hours post-dosing. The results are shown in Table 13 and 14.

Table 13: Single-dose pharmacokinetics of turoctocog alfa in young children with haemophilia A (0–<6 years) (NN7008-3545) – Full analysis set, dose-adjusted

NN7008-3545	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)
t½ (h)	7.65 (1.84)	9.99 (1.71)
Vss (mL/kg)	57.30 (26.75)	55.79 (23.71)
Cmax (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 14: Single-dose pharmacokinetics of turoctocog alfa in older children with haemophilia A (6–<12 years) (NN7008-3545) – Full analysis set, dose-adjusted

NN7008-3545 6–<12 years	Clotting assay N=14 Mean (SD)	Chromogenic assay N=14 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)
t½ (h)	8.02 (1.89)	9.42 (1.52)
Vss (mL/kg)	46.82 (10.62)	41.23 (6.00)
Cmax (IU/mL)	1.07 (0.35)	1.25 (0.27)
MRT (h)	9.91 (2.57	11.61 (2.32)
≥ 12 years	n=33 Mean (SD)	n=48 Mean (SD)
Incremental recovery (IU/mL)/(IU/kg)	0.022 (0.004)	0.029 (0.006)
AUC (IU*h/mL)	15.26 (5.77)	19.63 (7.73)
Total CL (mL/h)	3.63 (1.09)	2.86 (0.94)
t½ (h)	11.00 (4.65)	11.22 (6.86)
Vss (mL/kg)	47.40 (9.21)	38.18 (10.24)
Cmax (IU/mL)	1.226 (0.41)	1.63 (0.50)
MRT (h)	14.19 (5.08)	14.54 (5.77)

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

The mean AUC in young children and older children was 30% and 22% lower than in adults in NN7008-3522 (14.22 IU*h/mL) when using the clotting assay and 35% and 23% lower than in adults (18.70 IU*h/mL) when using the chromogenic assay.

Accordingly, the CL of turoctocog alfa was higher in children compared to adults: the mean CL in young children and older children was 67% and 34% higher than in adults in Trial 3522 (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 t½ of turoctocog alfa in young children and older children was 29% and 26% shorter than in adults in NN7008-3522 (10.83 hours) when using the clotting assay and 0.4% and 6% shorter than in adults (10.04 hours) when using the chromogenic assay.

Two patients did not participate in the pharmacokinetic session with previous product due to available historical pharmacokinetic data. However, historical data of both patients were excluded because of questionable quality.

A pharmacokinetic assessment of the patient's previous FVIII product was also investigated prior to first administration of turoctocog alfa. Each patient received one dose of their previous FVIII product (50 IU/kg) and one dose of turoctocog alfa (50 IU/kg) in this trial. In a post-hoc statistical analysis, the 90% confidence interval for all primary endpoints were within the interval of 0.8– 1.25, with the exception of the incremental recovery which was slightly lower for the previous product in the chromogenic assay as compared to turoctocog alfa.

Supportive pharmacokinetic data

Study NN7008-3893: In this multi-centre, open-label trial the PK of two production lots of turoctocog alfa was investigated in four adult patients with severe haemophilia A. The results are shown in Table 15.

Table 15: Single-dose pharmacokinetics of turoctocog alfa in adult patients with haemophilia A – Supportive data (Trial NN7008-3893) – Full analysis set, dose-adjusted

Trial NN7008-3893	**Clotting assay**	**Chromogenic assay**
	Mean (SD)	**Mean (SD)**
Incremental recovery (IU/mL)/(IU/kg)	0.024 (0.007)	0.031 (0.009)
AUC (IU*h/mL)	16.68 (3.26)	24.71 (6.26)
Total CL (mL/h)	182.9 (39.5)	124.8 (29.0)
Weight-normalised CL (mL/h/kg)	3.08 (0.56)	2.10 (0.43)
t½ (h)	11.16 (2.79)	13.00 (2.44)
Vss (mL/kg)	44.90 (14.83)	35.44 (13.09)
Cmax (IU/mL)	1.26 (0.41)	1.81 (0.66)
MRT (h)	14.41 (3.46)	16.52 (3.76)

Dose: 50 IU/kg turoctocog alfa (single i.v. dose); N=4

Dose proportionality and time dependencies

The strength of 3000 IU of the turoctocog alfa drug product has been investigated in a recently completed clinical trial (NN7008-4015). The trial design is outlined below.

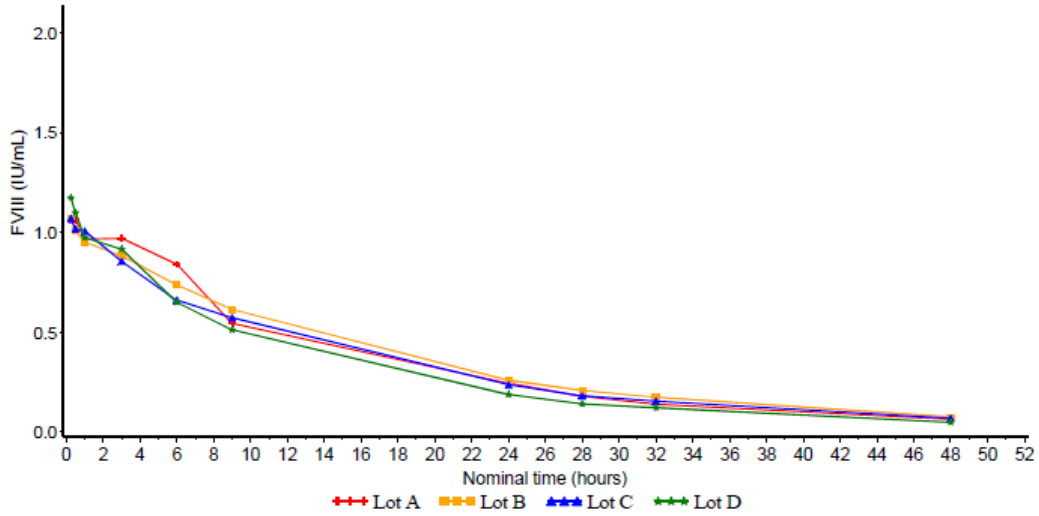
Trial 4015 was a multi-centre, randomised open-labelled trial investigating the PK of 4 lots of turoctocog alfa (3 lots of 2000 IU/vial and 1 lot of 3000 IU/vial) in patients with severe haemophilia A (FVIII<1%). The trial was performed as a two-period, incomplete block, cross-over trial, where each patient was randomised to receive two different lots of turoctocog alfa. None of the patients had previously participated in the clinical development programme for turoctocog alfa. A total of 15 patients completed the trial.

The trial included two PK sessions (Visits 2 and 3) and prior to each of these visits there was a wash-out period of at least 4 days since the last FVIII dosing. At each of the two PK sessions, the patients received a single i.v. dose of 50 IU/kg turoctocog alfa. Different combinations of the 4 lots (A, B, C and D) were administered to different patients, so that each patient received two different lots (one at Visit 2 and one at Visit 3) and all combinations of the 4 lots were represented in the trial population. The period between each visit was to be kept as short as possible. Blood samples for assessment of PK were taken at the PK sessions at pre-dose and at 10 time points up to 48 hours after administration of turoctocog alfa. Blood samples for assessment of FVIII inhibitors were collected at screening (Visit 1), pre-dosing at Visits 2 and 3, as well as 48 hours after dosing at Visit 3.

Each of the three 2000 IU lots was compared to the two other 2000 IU lots and 2-sided 90% confidence intervals were provided. In addition, test for difference between the three 2000 IU lots were performed and if these were not statistically different at the 5% level, the three 2000 IU lots were pooled and compared to the 3000 IU lot.

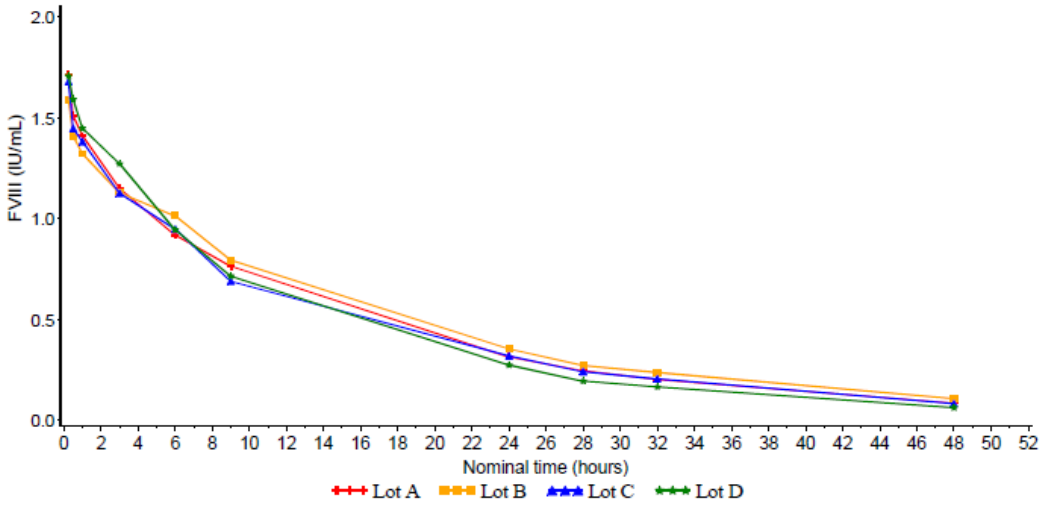
The results are presented in Figure 3 and 4.

Figure 3: Mean profiles for FVIII activity (dose-adjusted) for 2000 IU (lots A,B and C) and 3000 IU (lot D) of turoctocog alfa – clotting assay – full analysis set



Dose: 50 IU/kg turoctocog alfa (single i.v. dose)

Figure 4: Mean profiles of FVIII activity (dose-adjusted) for 2000 IU (lots A, B, C) and 3000 IU lot (lot D) of turoctocog alfa – chromogenic assay – full analysis set



Dose: 50 IU/kg turoctocog alfa (single i.v. dose)

Cross-reference: Appendix I, Figure 4

Figure 5 Mean profiles of FVIII activity (dose-adjusted) for 2000 IU lots (lots A, B and C) and 3000 IU lot (lot D) of turoctocog alfa – chromogenic assay – full analysis set

Special populations

The trials were global and included patients from Germany, Israel, Italy, Japan, Lithuania, Macedonia, Malaysia, Poland, Russian Federation, Switzerland, Turkey, the UK and the US. The majority of the patients included in the trials were White (23/33 adults/adolescent and 23/28 children) and of non-Hispanic or Latino ethnicity.

Japanese patients

Study NN7008-3600: Study NN7008-3600 was conducted in Japanese patients. This was an open-level, single-dose study to investigate the pharmacokinetic properties of turoctocog alfa in 6 Japanese patients with haemophilia A. The results are shown in Table 16.

Table 16: Single-dose pharmacokinetics of turoctocog alfa in Japanese patients with haemophilia A (Trial 3600) – Full analysis set, dose-adjusted

Trial NN7008-3600	**Clotting assay**	**Chromogenic assay**
	Mean (SD)	**Mean (SD)**
Incremental recovery(IU/mL)/(IU/kg)	0.024 (0.005)	0.033 (0.007)
AUC (IU*h/mL)	23.14 (10.81)	29.40 (13.23)
Total CL (mL/h)	161.9 (64.8)	124.1 (47.0)
Weight-normalised CL (mL/h/kg)	2.54 (1.06)	1.93 (0.64)
t½ (h)	12.61 (5.07)	15.46 (6.76)
V_{ss} (mL/kg)	37.51 (8.59)	33.76 (7.37)
C_{max} IU/mL)	1.38 0.37)	1.84 (0.37)
MRT (h)	17.12 (7.63)	20.36 (10.57)

Dose: 50 IU/kg turoctocog alfa (single i.v. dose); N=6

Adolescent patients (12–<18 years)

Two adolescent patients (13 and 17 years old) were included in the pharmacokinetic evaluation in Trials 3522 and 3543. The results are shown in Table 17 and 18.

Table 17: Single-dose pharmacokinetics of turoctocog alfa in 2 adolescent patients, children and adults with haemophilia A – clotting assay – full analysis set, dose-adjusted and excluding outliers

	0– <12 years (N=28) Mean (SD)a	≥18 years (N=31) Mean (SD)b	Patient 201001 (13 years) Mean (SD)c	Patient 201002 (17 years) Mean (SD)c
AUC (IU*h/mL)	10.50 (3.90)	15.13 (5.97)	16.90 (3.19)	16.44 (3.38)
t½ (h)	7.84 (1.84)	10.77 (4.78)	14.25 (0.06)	12.62 (2.58)
Incremental recovery	0.019 (0.006)	0.022 (0.004)	0.021 (0.004)	0.021 (0.004)
Total CL (mL/h)	134.0 (77.55)	266.5 (100.75)	204.1 (30.16)	174.0 (35.80)
Weight normalised CL (mL/h/kg)	5.61 (2.86)	3.68 (1.12)	3.01 (0.57)	3.11 (0.64)

Dose: 50 IU/kg turoctocog alfa (single i.v. dose)
[a]Data from Trials 3522, 3893, 3600, 3543 and 3545 (patients >18 years)
[b]Data from Trial 3545 (patients 0–12 years)
[c]Data from Trials 3522 and 3543 (adolescent patients)

Table 18: Single-dose pharmacokinetics of turoctocog alfa in 2 adolescent patients, children and adults with haemophilia A – chromogenic assay – full analysis set, dose- adjusted and excluding outliers

	0– <12 years (N=28) Mean (SD)a	≥18 years (N=31) Mean (SD)b	Patient 201001 (13 years) Mean (SD)c	Patient 201002 (17 years) Mean (SD)c
AUC (IU*h/mL)	13.30 (4.02)	19.28 (7.96)	24.43 (2.41)	22.56 (3.41)
t½ (h)	9.71 (1.62)	11.17 (7.16)	12.72 (0.25)	10.91 (0.81)
Incremental recovery	0.024 (0.006)	0.029 (0.006)	0.029 (0.003)	0.029 (0.004)
Total CL (mL/h)	98.19 (45.16)	212.3 (84.68)	139.6 (7.97)	125.5 (18.97)
Weight normalised CL (mL/h/kg)	4.14 (1.46)	2.93 (0.96)	2.06 (0.20)	2.24 (0.34)

Dose: 50 IU/kg turoctocog alfa (single i.v. dose)
[a]Data from Trials 3522, 3893, 3600, 3543 and 3545 (patients >18 years)
[b]Data from Trial 3545 (patients 0–12 years)
[c]Data from Trials 3522 and 3543 (adolescent patients)

2.4.3. Pharmacodynamics

No pharmacodynamics studies have been submitted.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetic parameters of turoctocog alfa were based on FVIII activity (FVIII:C) measurements. This parameter is known to correlate to clinical efficacy of FVIII products.

All pharmacokinetic studies with turoctocog alfa were conducted in previously treated patients with severe haemophilia A (FVIII ≤1%). The analysis of plasma samples (turoctocog alfa activity) was conducted using both the one-stage clotting assay and the chromogenic assay.

In an international study involving 36 laboratories, the assay performance of NovoEight in FVIII:C assays was evaluated and compared to a marketed full length recombinant FVIII product. The study showed that comparable and consistent results were obtained for both products and that NovoEight can be reliably measured in plasma without the need of a separate NovoEight standard.

The patient population, number of subjects, dose of recombinant factor VIII, evaluated PK parameters, sampling time points, applied assays and number of lots (three) used in these clinical studies complied with the *Guideline on clinical investigation of recombinant and human plasma-derived factor VIII products* (EMA/CHMP/BP*W*P/144533/2009). The comparison between 250 IU and 3000 IU, strength which is also intended to be marketed, was not performed as recommended in the guideline. However, the applicant did provide data in the paediatric trial that no statistical difference was observed in values for incremental recovery after dosing with turoctocog alfa from either 250 IU/vial or 2000 IU/vial. Further, the current data of the recently completed clinical trial (NN7008-4015) investigating the PK of 4 lots of turoctocog alfa (3 lots of 2000 IU/vial and 1 lot of 3000 IU/vial) showed that there was no difference between the pooled 2000 IU lots compared to the 3000 IU lot for both chromogenic and clotting assay, respectively. Therefore, it can be concluded that the PK characteristics of turoctocog alfa were not influenced by the strength.

Pharmacokinetics of turoctocog alfa was evaluated in five trials (first human dose trial, PK trial for two lots, PK in Japanese patients, pivotal phase 3 trial, paediatric trial) in a total of 61 previously treated male patients with severe haemophilia A from 1 to 54 years of age.

In the first human dose trial (Trial NN7008-3522), the PK of turoctocog alfa was compared to the pharmacokinetics of Advate. The pharmacokinetic assessment of turoctocog alfa was investigated after single intravenous (i.v.) dose of 50 IU/kg body weight and blood sampling was done at regular intervals throughout a 48-hour period. Overall, the average PK characteristics of turoctocog alfa seemed to be comparable to those of Advate to a 90% confidence interval analysis.

A repeat PK analysis was carried out in 15 subjects as Part A (PK session) of the pivotal phase 3 Trial NN7008-3543. Study subjects were given a single dose of 50 IU/kg of turoctocog alfa after 3-6 months of preventive dosing. The pharmacokinetic results 3– 6 months after the first injection of turoctocog alfa, as measured in Trial NN7008-3543, are considered comparable to the results obtained after the first dose of turoctocog alfa in Trial NN7008-3522. There is no indication for lower FVIII activity indicating a possible formation of inhibitory FVIII antibodies after multiple exposures. The applicant has submitted all the relevant data on the exclusion of four outliers. The data was considered acceptable. The differences in pharmacokinetic endpoints in study NN7008-3893 were mainly ascribed to slightly higher FVIII activity levels. There were also differences in the age-distribution of the patients, the mean age of the patients included in Trial 3893 was 33 years, whereas the mean age of the patients included in Trial 3522 was 24 years.

In Study NN7009-3545 the PK in children (< 12 years) was investigated. It complies with the requirements of the guideline (EMA/CHMP/BPWP/144533/2009) and the agreed PIP. The results of the pharmacokinetic parameters are comparable between young children and older children. The lower AUC, higher CL and lower t½ seen in children in comparison to adults with haemophilia A following administration of turoctocog alfa have also been described for other FVIII products. There are only very

small differences in mean $t_{1/2}$ between children and adults comparing the results of the chromogenic assay. In addition, the pharmacokinetic profiles of turoctocog alfa were quite similar to the pharmacokinetic profiles of the patients' previous FVIII products in children with haemophilia A as also investigated in this trial. Overall, the observed variations of parameters e.g. incremental recovery in the post-hoc analysis are acceptable with regard to the pool of different previous products. The PK characteristics for the two adolescent patients correlate very well with the data of adults. The half-lives are markedly prolonged in comparison to the children's population.

The pharmacokinetic parameters were comparable between paediatric patients below 6 years of age and the paediatric patients from 6 to below 12 years of age. Some variation was observed in the pharmacokinetic parameters of turoctocog alfa between paediatric and adult patients. The higher CL and the shorter $t_{½}$ seen in paediatric patients compared to adult patients with haemophilia A may be due in part to the known higher plasma volume per kilogram body weight in younger patients.

Pharmacokinetic characteristics of turoctocog alfa have not been studied in the following special populations: 1) Previously untreated patients; 2) Subjects over 65 years of age; 3) Subjects with impaired renal function; 4) Subjects with impaired hepatic function. The effects of ethnic background on PK characteristics have only been studied in Japanese patients.

The justification of the applicant for not conducting dedicated PD studies was acceptable.

In the first human dose trial NN7008-3522 there have been numerous protocol violations. Hence, the applicant identified some outliers based on following criteria: pre-dosing activity >5% due to inadequate wash-out, deviation of administered dose > 20% and profiles not indicative of a normal i.v. bolus administration. The post-hoc defined criteria are understood and the study can still be regarded as valid. PK characteristics [mean (range)] of turoctocog alfa in the pivotal PK trial (NN7008-3522) were for the chromogenic assay in a total of 20 patients (full analysis set, adjusted for dose and excluding outliers): Incremental recovery IU/mL/IU/kg 0.028 (0.006); Terminal half-life h 10.04 (3.59); AUC IU/mL 18.70 (5.08); Total Clearance mL/h 209.7 (67.15).

PK has been evaluated in only two adolescent patients (13 and 17 years old) in the studies NN7008-3522 and NN7008-3543. According to the guideline, PK evaluation in adolescent patients is not explicitly required. The results for these two patients were within the range of the results for adult patients above 18 years in Trial NN7008-3522.

The lack of interaction studies are acceptable as no interaction is expected and thus, they are not required. The FVIII measurements, as used for pharmacokinetic assessment, are known to correlate to clinical efficacy of FVIII products. Thus, the coagulation activities are to be considered as pharmacodynamic in nature, as they reflect the biologic response to turoctocog alfa and thus no PD studies are required. This is considered acceptable.

2.4.5. Conclusions on clinical pharmacology

Overall, the data on pharmacokinetic of turoctocog alfa in adults, adolescent patients and children with severe Haemophilia A is regarded acceptable and comparable with other FVIII products. Concerns regarding the numerous protocol violations in PK study NN7008-3522 and the exclusion of outliers have been addressed satisfactorily.

The dosage and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of the bleeding and the patient's clinical condition.

The number of units of factor VIII is expressed in International Units (IU), which are related to the current WHO standard for factor VIII products. The activity of factor VIII in plasma is expressed either as percentage (relative to normal level human plasma) or in International Units (relative to an International Standard for factor VIII in plasma).

One International Unit (IU) of factor VIII activity is equivalent to that quantity of factor VIII in one ml normal human plasma.

On demand treatment

The calculation of the required dose of factor VIII is based on the empirical finding that 1 International Unit (IU) factor VIII per kg body weight raises the plasma factor VIII activity by 2 IU/dl. The required dose is determined using the following formula:

Required units = body weight (kg) x desired factor VIII rise (%) (IU/dl) x 0.5 (IU/kg per IU/dl).

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

In the case of the following haemorrhagic events, the factor VIII activity should not fall below the given plasma activity level (in % of normal or IU/dl) in the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery:

Degree of haemorrhage/ Type of surgical procedure	FVIII level required (%) (IU/dl)	Frequency of doses (hours)/ Duration of therapy (days)
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20-40	Repeat every 12 to 24 hours, at least 1 day, until the bleeding episode as indicated by pain is resolved or healing achieved
More extensive haemarthrosis, muscle bleeding or haematoma	30-60	Repeat infusion every 12-24 hours for 3-4 days or more until pain and acute disability are resolved
Life threatening haemorrhages	60-100	Repeat infusion every 8 to 24 hours until threat is resolved
Surgery		
Minor surgery including tooth extraction	30-60	Every 24 hours, at least 1 day,until healing is achieved
Major surgery	80-100 (pre- and postoperative)	Repeat infusion every 8-24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dl)

Prophylaxis

For long term prophylaxis against bleeding in patients with severe haemophilia A. The usual recommended doses are 20-40 IU of factor VIII per kg body weight every second day or 20-50 IU of factor VIII per kg body weight 3 times weekly. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

Treatment monitoring

During the course of treatment, appropriate determination of factor VIII levels is advised to guide the dose to be administered and the frequency of repeated injections. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable. Individual patients may vary in their response to factor VIII, achieving different levels of in vivo recovery and demonstrating different half-lives.

Surgery

There is no experience in surgery of paediatric patients.

Older people

There is no experience in patients > 65 years.

Paediatric population

For long term prophylaxis against bleeding in patients below the age of 12, doses of 25-50 IU of factor VIII per kg body weight every second day or 25-60 IU of factor VIII per kg body weight 3 times weekly

are recommended. For paediatric patients above the age of 12 the dose recommendations are the same as for adults.

The methos of administration of turoctocog alfa is intravenous use.

The recommended infusion rate for NovoEight is 1-2 ml/min. The rate should be determined by the patient's comfort level.

For instructions on reconstitution of the medicinal product before administration, see section 6.6 of the SmPC.

2.5. Clinical efficacy

The clinical efficacy of turoctocog alfa was investigated in three studies, the main pivotal study NN7008-3543, the paediatric study N7008-3545 and the extension study N007-3568. The flow of patients in the clinical development programme is presented in Figure 5.

Figure 5: Flow of patients in the clinical development programme for turoctocog alfa:

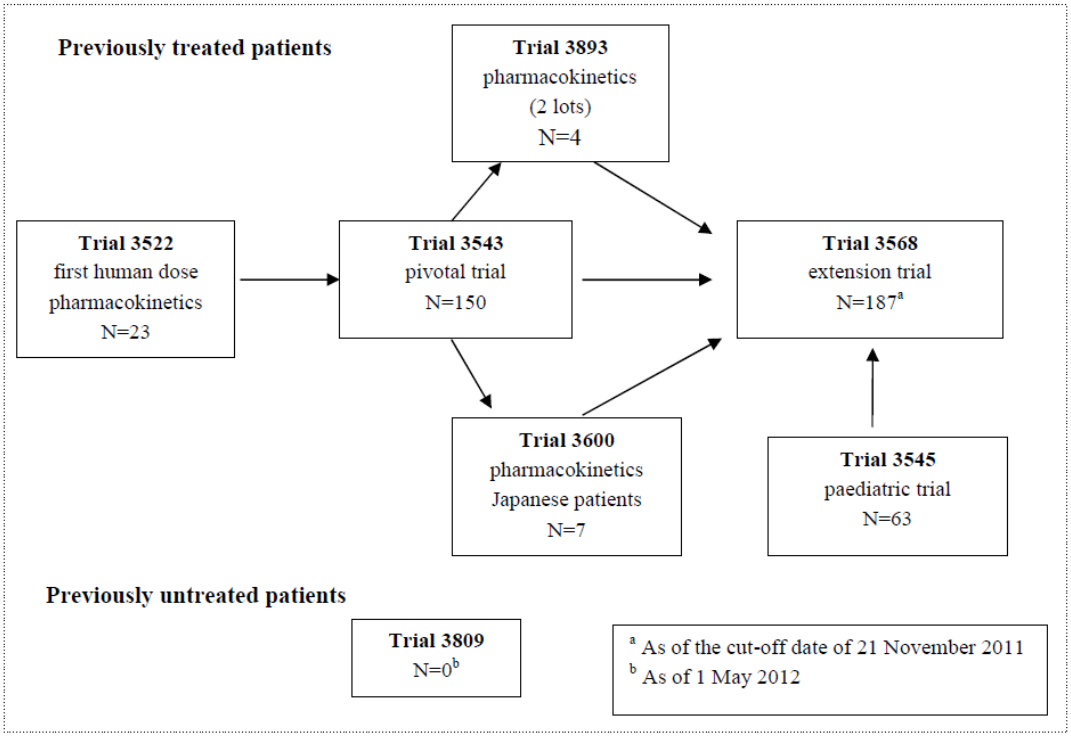


Figure 1-1 Flow of patients in the clinical development programme for turoctocog alfa

2.5.1. Dose response study

No dose response study was submitted.

2.5.2. Main studies

Study NN7008-3543: A multi-centre, open-label, non-controlled trial on safety and efficacy of turoctocog alfa in prevention and treatment of bleeds in previously treated patients with haemophilia A

Sub-trial: Safety and efficacy of turoctocog alfa in prevention and treatment of bleeding during surgical procedures in patients with haemophilia A

Methods

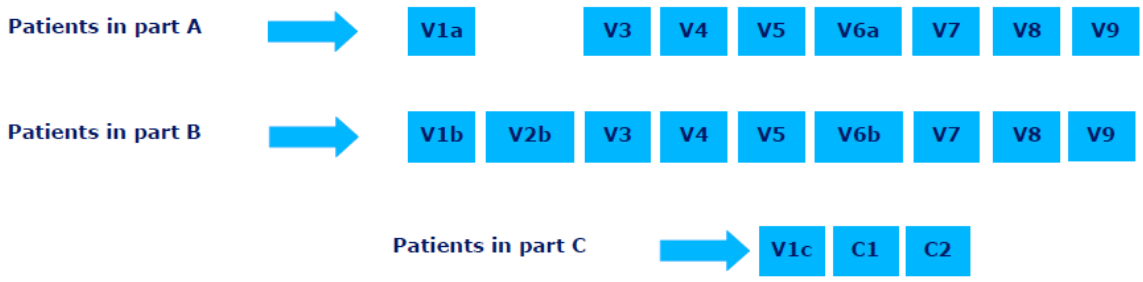
The trial was designed as a multi-centre, multi-national, open-label, single-arm efficacy and safety trial in patients with haemophilia A and a FVIII activity ≤1%.

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.



Study Participants

Inclusion criteria – Part A

1. Completion of the phase 1 pharmacokinetic trial (NN7008-3522).

2. Informed consent obtained prior to any trial-related activities. (Trial-related activities are any procedure that would not have been performed during normal management of the patient).

3. Male patients with the diagnosis of severe (FVIII≤1%) haemophilia A from age 12 years (except for Israel where the age limit will be 18 years for the first 10 patients recruited in the trial) to 56 years having a weight of 10 to 120 kg.

4. Willing to undergo a bleeding preventive treatment of 75 exposure days (EDs).

5. Non-bleeding state (i.e. no clinical manifestation of active bleed) at the time of administration of trial product for measurement of recovery in relation to administration of the first dose and the pharmacokinetic session.

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

7. No history of FVIII inhibitors ≥0.6 BU. The inhibitor should be measured regularly for at least the last 8 years or since the first treatment of haemophilia A.

8. No detectable inhibitors to FVIII (≥0.6 BU) (as assessed by a central laboratory at the time of screening).

9. With Amendment 14, this inclusion criterion was deleted "Hepatitis C Virus (HCV) seronegative or if HCV seropositive, viral load less than 200 particles/µL measured by PCR".

10. With Amendment 14, this inclusion criterion was deleted: "Lupus anticoagulant negative".

11. HIV-1 seronegative or if HIV-1 seropositive, viral load < 400.000 copies/mL and CD4+ lymphocyte count ≥200/µL.

Inclusion criteria Part B

1. Informed consent obtained prior to any trial-related activities (Trial-related activities are any procedure that would not have been performed during normal management of the patient).

2. Male patients with the diagnosis of severe (FVIII≤1%) haemophilia A from age 12 years (*except for Israel where the age limit will be 18 years for the first 10 patients recruited in the trial and 18 years for all patients in Croatia*) to 65 years having a weight of 10 (*20 in Brazil*) to 120 kg.

The text above in italics was added with Amendment 14.

3. Willing to undergo a bleeding preventive treatment of 75 exposure days.

4. Non-bleeding state (i.e. no clinical manifestation of active bleed) at the time of administration of trial product for measurement of recovery in relation to administration of the first dose.

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

6. No prior history of FVIII inhibitors. *Documentation should be available for at least the last 8 years (or since treatment with FVIII products started if shorter than 8 years).* The text above in italics was modified with Amendment 17. Prior to Amendment 17, the inhibitor cut-off value was 0.6 BU. However, some local laboratories could not measure values below 1 BU and with Amendment 17 it was decided to remove the cut-off value of 0.6 BU from this inclusion criterion.

7. No detectable inhibitors to FVIII (≤0.6 BU) (as assessed by a central laboratory at the time of screening).

8. With Amendment 14, this inclusion criterion was deleted: "Hepatitis C Virus (HCV) seronegative or if HCV seropositive, viral load less than 200 particles/µL measured by PCR".

9. With Amendment 14, this inclusion criterion was deleted: "Lupus anticoagulant negative".

10. HIV-1 seronegative or if HIV-1 seropositive, HIV viral load < 400.000 copies/mL and CD4+ lymphocyte count ≥200/µL.

Inclusion criteria for Part C

1. Undergo major or minor surgical procedures.

2. Surgical procedure requiring at least 7 days of infusion of turoctocog alfa post-operatively.

Patients will only participate in part C when they have been included in either part A or part B and have received at least one dose of trial product (turoctocog alfa). *Patients can be recruited into part C when at least 5 patients have each been treated with turoctocog alfa for a bleed and 80% of these patients have a response rated excellent or good on the four–point haemostatic response scale for their first bleed.*

With Amendment 14, the text above in italics was added.

Exclusion criteria

Part A and B

1. Patients receiving immune *modulating medication* or tolerance induction (ITI) regimens.

With Amendment 9, the text above in italics was added.

2. Factor replacement treatment of a mild or moderate bleed within 3 days prior to first dose (*only applicable for patients in part B*).

With Amendment 9, the text above in italics was added.

3. Factor replacement treatment of a severe bleed within one week prior to first dose (*only applicable for patients in part B*).

With Amendment 9, the text above in italics was added.

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.*

With Amendment 9, the text above in italics was added.

6. Severe current hepatic dysfunction or severe hepatic disease during the last 12 months.

7. ALT > 4 times the upper limit of normal reference range (as defined by central laboratory ranges) (*only for patients in part A*).

With Amendment 9, the text above in italics was added.

8. Febrile illness within 5 days prior to the first trial product administration and pharmacokinetic dosing

9. Current dialysis therapy.

10. Creatinine levels 50% above normal level (as defined by normal reference range at central laboratory).

11. Congenital or acquired coagulation disorders other than haemophilia A.

12. Previous arterial thrombotic events (myocardial infarction and intra-cranial thrombosis) (as defined by medical records).

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

14. Surgery within one month prior to first administration of trial product (catheter, stents, ports, and dental extractions do not count as surgeries [i.e. they will not exclude the patient]).

15. Use of coagulation factors *other than turoctocog alfa*: Commercial FVIII concentrates or other FVIII containing products within 48 hours prior to first administration of trial product *for recovery assessment. (Not applicable for part A patients 1-3).*

With Amendments 9 and 14, the text above in italics was added.

16. Use of anticoagulants: Heparin, vitamin-K antagonists, and direct thrombin inhibitors one week prior to first administration of trial product.

17. With Amendment 9, this exclusion criterion was deleted: “Use of non-prescribed opiate substances”.

18. With Amendment 9, this exclusion criterion was deleted: “Regular use of cannabis (only for patients in part A)”.

19. Use of platelet inhibitors including NSAID one week prior to first administration of trial product (*only for patients in part A*).

With Amendment 9, the text above in italics was added.

20. The receipt of any investigational drug within 30 days prior to administration of trial product except patients who have completed NN7008-3522 (*for Brazil within one year prior to screening for this trial, unless there, in the investigators opinion, is a direct benefit to the research patient*).

With Amendments 11 and 14, the text above in italics was added.

21. Previous participation in the current trial (defined as withdrawal) or withdrawn patients from NN7008-3522 after administration of trial product.

22. Any disease or condition which, according to the investigator’s judgement, could imply a potential hazard to the patient, interfere with the trial participation or trial outcome.

23. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation.

Treatments

Preventive treatment and dose adjustments

This was a single arm trial with all patients receiving prophylactic FVIII treatment. The initial dose was 20 IU/kg administered every second day or three times per week to achieve a trough level ≥0.01 IU/mL or above the assay lower limit of quantification (LLoQ) of the clinic. The frequency of dosing (either every second day or three times per week) was selected at the investigator’s discretion. The frequency of dosing could be changed at a visit if deemed necessary by the investigator. If the trough level was

below the assay LLoQ of the clinic, the dose level could be increased by 5 IU/kg as decided by the investigator to a level that secured prevention of bleeds.

Dose adjustments could be performed at planned as well as at unscheduled visits. If the trough level was ≥0.01 IU/mL or above the assay LLoQ of the clinic and a bleed occurred, the dose level was recommended to be increased until no bleeding occurred as assessed clinically by the investigator.

The bleeding preventive treatment was home treatment with i.v. self-injection by the patient or a support person.

Treatment of bleeds and dose adjustments

In case of acute mild/moderate bleeds, the standard treatment was dosing of turoctocog alfa to aim at a post-infusion turoctocog alfa level of at least 0.50 IU/mL that could be repeated, if needed. All bleeds had to be reported to the site within 24 hours. For treatment of a severe bleed, doses up to 200 IU/kg per day could be used at the discretion of the investigator.

If the effect of turoctocog alfa on the bleed was insufficient, another FVIII product could be selected at the discretion of the investigator. If treatment with another FVIII product was initiated, the patient was to be withdrawn from the trial.

Treatment of patients who participated in part C (Visit C1 and Visit C2)

Trial periods during surgery

The trial period for the individual patient was divided into two time periods

- Surgery period (C1) consisted of pre-surgery Day, Day 1, Day 2, Day 3, Day 4, Day 5, Day 6 and Day 7 where Day 1 was the day of surgery.
- Surgical recovery period (C2) consisted of Day 8 and until it was deemed the last appropriate day for trial product infusion after surgery (return to preventive treatment).

Dose adjustments during surgery

Loading dose: All patients received a preoperative loading dose of turoctocog alfa immediately prior to the surgical procedure. The dose was according to the standard practice at the site.

Surgery period: On the day of surgery and until Day 7 (included): turoctocog alfa was dose adjusted aiming for a trough level above 0.50 IU/mL.

Surgical recovery period: Day 8 to last day of the surgical recovery period (if relevant): turoctocog alfa was dosed according to local guidelines.

Objectives

Primary objective for part A, part B and part C

- To assess the incidence rate of FVIII inhibitors (≥ 0.6 BU)

Secondary objectives of part A and part B

- To evaluate the clinical efficacy of turoctocog alfa in bleeding prevention in patients with haemophilia A
- To evaluate the clinical efficacy of turoctocog alfa when treating bleeds in patients with haemophilia A
- To evaluate the safety of turoctocog alfa when used for prevention of bleeds and treatment of mild/moderate and severe bleeds in patients with haemophilia A
- To assess changes in patient-reported outcomes (PROs) from screening to end of trial
- Part A only: To describe and compare the pharmacokinetic profile of turoctocog alfa in the patients who participated in both this trial and NN7008-3522

Secondary objectives of part C

- To evaluate the efficacy of turoctocog alfa during surgical procedures in patients with haemophilia A
- To evaluate the haemostatic response to turoctocog alfa in the post-surgery period for patients with haemophilia 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 patients with haemophilia A
- To assess changes in PROs from pre-surgery to last day of the surgical recovery period

Outcomes/endpoints

Primary endpoint

- The incidence rate of FVIII inhibitors (≥ 0.6 BU)

Secondary efficacy endpoints

Part A and part B

Bleeding prevention

- Total consumption of turoctocog alfa per patient (prevention and treatment of bleeds) per month
- Actual consumption of turoctocog alfa (IU/kg /month) for prevention
- Average number of bleeds per month

Treatment of bleeds

- Haemostatic effect of turoctocog alfa evaluated according to a predefined four grade scale: None, moderate, good or excellent.
- The 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. If the haemostatic response was rated as excellent or good, the treatment of the bleed was considered a success. If the haemostatic response was rated as moderate or none, the treatment was considered a failure.
- 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
- Haemoglobin level prior to surgery, during, and after surgery (pre-operative, intra-operative, and post-operative)
- Blood product transfusion

Patient-reported outcomes

Several questionnaires were used to assess disease and age-group specific quality of life (QOL) and treatment satisfaction: age specific versions of HAEMO-QOL HEMO-SAT, EQ-5D (European Quality of Life - 5 Dimensions) were used.

Sample size

To be able to conclude adequate safety with regard to inhibitor formation the upper 1-sided 97.5% confidence limit for the incidence rate of FVIII inhibitor needed to be below 6.8%. If 3 inhibitors out of 127 patients were observed the upper 1-sided 97.5% confidence limit was below 6.8%. In order to allow for a 10% withdrawal rate before the 50 exposure days, the trial was planned to have 140 patients dosed with turoctocog alfa. If the true inhibitor rate was 2% (in line with what has been seen for other FVIII products) then the chance of seeing 3 or less inhibitors out of 140 dosed patients was 69%. Therefore, the trial aimed to dose approximately 140 patients and to have 127 patients with a minimum of 50 exposure days.

Randomisation

The patients were not randomised as this is a single arm trial.

Blinding (masking)

The patients were not blinded as this is an open label trial.

Statistical methods

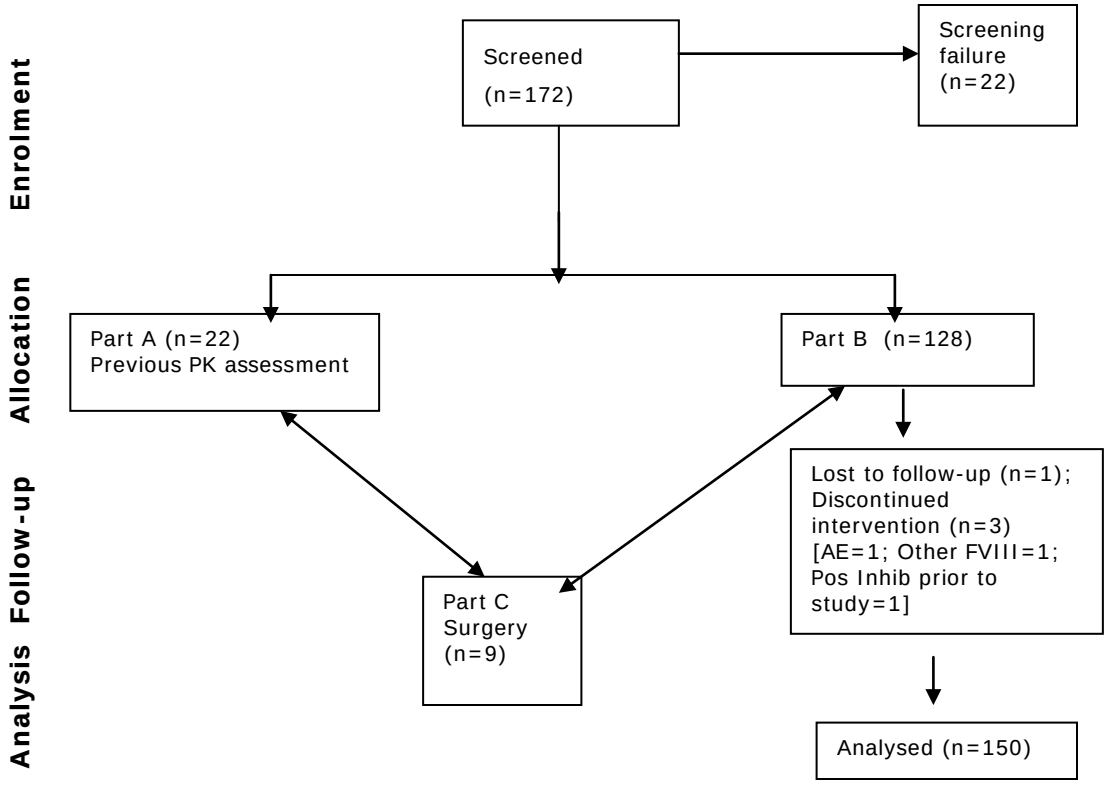
Aside the analysis for antibody development, the most important efficacy endpoint for bleeding prevention was the annualised bleeding rate. This was estimated using a Poisson model allowing for overdispersion. Haemostatic effect of turoctocog alfa was evaluated according to a predefined

four-grade scale: None, moderate, good or excellent, and was to be 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.

Data arising from other endpoints were analysed in a descriptive manner.

Results

Participant flow



Recruitment

The study initiated on 7 April 2009 (first patient first visit) and had the last patient visit on the 21 September 2011.

Conduct of the study

There were 22 substantial amendments to the protocol and some of these amendments changed the inclusion, exclusion and withdrawal criteria. The most important change occurred with amendment 14 after consultation with the FDA, which introduced a change in the primary endpoint from efficacy to safety.

There were in total 33 protocol deviations at the patient level. The distribution of the deviations is presented in Table 19.

Table 19: Protocol deviations on patient level

Deviation	Number of deviations
Inclusion/exclusion criteria	6
Withdrawal criteria	0
Informed consent	14
Laboratory samples	4
Assessment deviations	1
Treatment compliance	5
Trial product handling	0
Visit window	0
Other	3
Total	*33*

A total of 102 deviations were related to laboratory samples. Most of these were missing samples or samples taken outside of the sampling window. A total of 103 deviations were related to the assessments described in the protocol. Missed blood samples and blood samples taken outside the sampling window were also included in this category. A total of 71 deviations were reported in this category. These were mainly due to patients not following the dose regimen, patients taking wrong doses, issues with drug accountability and issues with IVRS/IWRS.

Baseline data

The demographics of the trial population and treatment history at baseline are presented in Tables 20 and 21 below.

Table 20: Demographics and baseline characteristics

	Part A	Part C	Total (Part A and Part B)
Number of patients	22	9	150
Age (years)			
N	22	9	150
Mean (SD)	24 (7.88)	25 (6.53)	28 (11.79)
Median	22	25	25
Min ; Max	13 ; 54	14 ; 36	12 ; 60
Country, N (%)			
N	22 (100.0)	9 (100.0)	150 (100.0)
Brazil	0 (0.0)	0 (0.0)	16 (10.7)
Croatia	0 (0.0)	0 (0.0)	11 (7.3)
Germany	3 (13.6)	0 (0.0)	10 (6.7)
Israel	11 (50.0)	1 (11.1)	12 (8.0)
Italy	6 (27.3)	0 (0.0)	7 (4.7)
Japan	0 (0.0)	0 (0.0)	9 (6.0)
Malaysia	0 (0.0)	0 (0.0)	5 (3.3)
Russian Federation	0 (0.0)	0 (0.0)	5 (3.3)
Serbia	0 (0.0)	2 (22.2)	19 (12.7)
Spain	0 (0.0)	0 (0.0)	4 (2.7)
Switzerland	2 (9.1)	1 (11.1)	5 (3.3)
Taiwan, Province of China	0 (0.0)	0 (0.0)	4 (2.7)
Turkey	0 (0.0)	1 (11.1)	11 (7.3)
United Kingdom	0 (0.0)	1 (11.1)	3 (2.0)
United States	0 (0.0)	3 (33.3)	29 (19.3)
Ethnicity, N (%)			
N	22 (100.0)	9 (100.0)	150 (100.0)
Hispanic Or Latino	0 (0.0)	0 (0.0)	25 (16.7)
Not Hispanic Or Latino	22 (100.0)	9 (100.0)	125 (83.3)
Race, N (%)			
N	22 (100.0)	9 (100.0)	150 (100.0)
White	21 (95.5)	9 (100.0)	121 (80.7)
Black Or African American	0 (0.0)	0 (0.0)	3 (2.0)
Asian	1 (4.5)	0 (0.0)	20 (13.3)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	6 (4.0)

Table 21: Treatment history – full analysis set

	Part A	Part C	Total (Part A and Par
Number of subjects	22	9	150
Type of treatment, N (%)			
Prophylaxis	13 (59.1)	7 (77.8)	91 (60.7)
Non-Prophylaxis	13 (59.1)	7 (77.8)	97 (64.7)
If Prophylaxis			
Number of month on prophylaxis			
N	13	7	91
Mean (SD)	80.8 (84.7)	74.7 (123.3)	78.6 (99.6)
Median	29.0	31.0	32.0
Min ; Max	4.0 ; 252.0	2.0 ; 348.0	2.0 ; 480.0
Dose level (IU/kg BW)			
N	13	7	91
Mean (SD)	28.5 (9.6)	28.4 (13.3)	25.3 (10.6)
Median	28.0	30.0	24.0
Min ; Max	12.5 ; 50.0	14.7 ; 50.0	7.0 ; 63.0
Frequency of dosing, N (%)			
N	13 (100.0)	7 (100.0)	91 (100.0)
Every 48 hours	1 (7.7)	1 (14.3)	11 (12.1)
Every 72 hours	3 (23.1)	0 (0.0)	22 (24.2)
Every 96 hours	0 (0.0)	0 (0.0)	2 (2.2)
Once every seven days	1 (7.7)	1 (14.3)	3 (3.3)
Other	8 (61.5)	5 (71.4)	53 (58.2)
FVIII product given, N (%)			
N	13 (100.0)	7 (100.0)	91 (100.0)
Recombinant FVIII product	7 (53.8)	4 (57.1)	42 (46.2)
Plasma FVIII product	6 (46.2)	3 (42.9)	49 (53.8)
Number of bleeds within the last 12 months			
N	13	7	91
Mean (SD)	6.0 (8.2)	9.1 (5.4)	8.9 (11.4)
Median	2.0	12.0	5.0
Min ; Max	0.0 ; 24.0	0.0 ; 14.0	0.0 ; 55.0
If Non-Prophylaxis			
Average number of bleeds per month within the last 12 months			
N	13	7	97
Mean (SD)	5.5 (5.2)	2.6 (2.7)	3.6 (3.3)
Median	3.0	2.0	2.0
Min ; Max	0.0 ; 18.0	0.0 ; 8.0	0.0 ; 18.0
FVIII product given, N (%)			
N	13 (100.0)	7 (100.0)	99 (100.0)
Recombinant FVIII product	2 (15.4)	3 (42.9)	27 (27.3)
Plasma FVIII product	11 (84.6)	4 (57.1)	72 (72.7)
Surgeries			
Number of major surgeries with the last 5 yrs			
N	5	5	30
Mean (SD)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)
Median	1.0	1.0	1.0
Min ; Max	1.0 ; 1.0	1.0 ; 1.0	1.0 ; 1.0

Treatment History - Full Analysis Set

	Part A	Part C	Total (Part A and Part B)
Surgeries			
FVIII product given, N (%)			
N	5 (100.0)	5 (100.0)	29 (100.0)
Recombinant FVIII product	2 (40.0)	4 (80.0)	12 (41.4)
Plasma FVIII product	2 (40.0)	1 (20.0)	16 (55.2)
NK	1 (20.0)	0 (0.0)	1 (3.4)
Exposure days			
Exposure days prior to trial entry			
N	22	9	149
Mean (SD)	669.7 (993.5)	677.9 (830.7)	875.3 (945.5)
Median	157.0	430.0	516.0
Min ; Max	151.0 ; 4225.0	151.0 ; 2809.0	150.0 ; 6441.0
Exposure days with prophylaxis prior to trial entry			
N	13	7	91
Mean (SD)	499.2 (636.3)	602.3 (981.7)	754.3 (851.2)
Median	151.0	274.0	408.0
Min ; Max	30.0 ; 2000.0	16.0 ; 2800.0	16.0 ; 3249.0
Exposure days with non-prophylaxis prior to trial entry			
N	13	7	97
Mean (SD)	631.0 (1188.7)	244.7 (189.6)	594.5 (738.4)
Median	151.0	151.0	276.0
Min ; Max	60.0 ; 4200.0	150.0 ; 656.0	36.0 ; 4200.0

Numbers analysed

Part A and B

All 150 patients who were dosed with turoctocog alfa were included in the full analysis set (FAS) on which all the efficacy analyses, including analyses of PRO, are based. None of the exposed patients were excluded from the analyses, except for the duration from first trial product administration to Visit 7 was used instead of during the entire period for one patient. This decision was made prior to database lock.

Part C

A total of 9 surgeries in 9 patients were performed during the trial. Eight of these were major surgeries and 1 was a minor surgery. Only one of the surgeries was done in an adolescent patient.

Outcomes and estimation

The majority of the patients (82.7%) followed the three times per week dosing schedule, 16.7% were dosed every second day and one patient (0.7%) changed dosing schedule from three times per week to every second day.

Consumption of turoctocog alfa

The mean total consumption per month per patient for prevention and treatment of bleeds was 338 IU/kg/patient ranging from 222 to 747 IU/kg/patient and higher for patients in good compliance than for patients who were less compliant. The mean total consumption for prevention, treatment of bleeds and surgery in the entire trial period was 2156 IU/kg/patient ranging from 256 to 5420 IU/kg/patient.

Prevention of bleeds

A total of 11873 preventive doses of turoctocog alfa were taken during the trial and the mean preventive dose was 24.4 IU/kg ranging from 12.8 to 97.4 U/kg. The mean consumption per month for prevention was 309 IU/kg/month and for patients in good compliance it was 313 IU/kg/month, while for patients who were less compliant it was 263 IU/kg/month. The same pattern was seen with the yearly consumption where the overall mean was 3812 IU/kg/year and 3841 IU/kg/year for patients in good compliance and 3412 IU/kg/year for patients who were less compliant.

Treatment of bleeds

A total of 813 doses were taken during the trial for treatment of 499 bleeds and the mean dose for treatment of a bleed was 30.4 IU/kg/dose ranging from 9.8 to 61.1 IU/kg/dose. The mean consumption used for treatment of bleeds (from start to stop of the bleed) was 45.6 IU/kg/bleed. The reason that the mean dose for treatment of a bleed was lower than the mean consumption from start to stop of a bleed was that some bleeds were treated with more than one dose. The mean consumption from the time the bleed stopped until the patient returned to preventive regimen was 14.2 IU/kg/bleed. The consumption of turoctocog alfa used for treatment of bleeds was slightly higher for patients in good compliance than for less compliant patients.

Efficacy of turoctocog alfa when used for prevention of bleeds

Annualised bleeding rates

The annualised bleeding rates were estimated using a Poisson model allowing for overdispersion and presented with a 95% confidence interval (95% CI). Almost one third of the patients did not have a bleed during the trial. The total estimated mean bleeding rate was 5.55 bleeds/patient/year for adolescents and 6.68 bleeds/patient/year for adults.

The estimated mean bleeding rate for spontaneous bleeds was 4.32 bleeds/patient/year (3.15 bleeds/patient/year for adolescents and 4.55 bleeds/patient/year for adults). The rate of traumatic bleeds was 2.07 bleeds/patient/year for adolescents and 1.53 bleeds/patient/year for adults.

The estimated mean bleeding rate for patients who were in good compliance was considerably lower (6.18 bleeds/patient/year) than for patients who were less compliant (10.55 bleeds/patient/year).

The estimated mean bleeding rate for all patients varied between the countries with the lowest bleeding rate in Japan (1.34 bleeds/patient/year) and the highest in the Russian Federation (23.22 bleeds/patient/year). The estimated bleeding rate among adolescents was also high in the Russian Federation (25.82 bleeds/patient/year), while in the remaining countries, that included adolescents, it was lower ranging from 0.0 in Spain to 5.89 bleeds/patient/year in US.

The total median bleeding rate was 3.66 bleeds/patient/year.

Table 23: Annualised bleeding rates – full analysis set

	[N] Estimated mean number of bleeds/patient/year (95% CI)		
	All patients	**Adolescent patients**	**Adult patients**
Total	[150] 6.50 (5.30–7.97)	[24] 5.55 (3.35–9.19)	[126] 6.68 (5.35–8.34)
By compliance			
Good compliance	[140] 6.18 (4.99–7.66)	[24] 5.55 (3.35–9.19)	[116] 6.31 (4.98–8.00)
Less compliance	[10] 10.55 (5.71–19.52)	–	[10] 10.55 (5.71–19.52)
By cause of bleed			
Spontaneous	[150] 4.32 (3.34–5.59)	[24] 3.15 (1.73–5.72)	[126] 4.55 (3.43–6.02)
Traumatic	[150] 1.62 (1.22–2.15)	[24] 2.07 (1.00–4.29)	[126] 1.53 (1.13–2.08)
Other	[150] 0.48 (0.29–0.79)	[24] 0.33 (0.11–1.03)	[126] 0.51 (0.30–0.87)
By country			
Brazil	[16] 3.43 (1.64–7.17)	[9] 5.03 (2.25–11.25)	[7] 1.46 (0.35–6.10)
Croatia	[11] 2.48 (0.80–7.70)	–	[11] 2.48 (0.80–7.70)
Germany	[10] 3.18 (1.33–7.58)	–	[10] 3.18 (1.33–7.58)
Israel	[12] 9.21 (5.34–15.89)	–	[12] 9.21 (5.34–15.89)
Italy	[7] 3.17 (1.73–5.84)	[2] 2.75 (0.36–20.83)	[5] 3.35 (1.76–6.37)
Japan	[9] 1.34 (0.54–3.31)	–	[9] 1.34 (0.54–3.31)
Malaysia	[5] 5.04 (1.83–13.84)	[1] 3.97 (0.99–15.88)	[4] 5.29 (1.55–18.13)
Russian Federation	[5] 23.22 (14.58–36.99)	[1] 25.82 (14.99–44.46)	[4] 22.57 (12.21–41.73)
Serbia	[19] 11.99 (7.58–18.94)	[5] 5.63 (1.53–20.76)	[14] 14.44 (9.08–22.96)
Spain	[4] 3.84 (0.79–18.75)	[1] 0.0 (0.0–0.0)	[3] 5.16 (1.13–23.64)
Switzerland	[5] 6.49 (4.52–9.31)	–	[5] 6.49 (4.52–9.31)
Taiwan	[4] 7.27 (2.62–20.14)	–	[4] 7.27 (2.62–20.14)
Turkey	[11] 6.05 (3.10–11.80)	[4] 4.75 (1.89–11.98)	[7] 6.82 (2.80–16.59)
UK	[3] 5.37 (3.02–9.53)	–	[3] 5.37 (3.02–9.53)
US	[29] 6.26 (4.19–9.36)	[1] 5.89 (1.90–18.27)	[28] 6.26 (4.17–9.40)

CI: confidence interval, N: number of patients

Efficacy of turoctocog alfa when used for treatment of acute bleeds

A total of 499 bleeds were treated during the trial. The majority of the bleeds (66.5%) were spontaneous, 24.8% were caused by trauma and 8.6% were of other origin or with missing information. The bleeds were classified as mild/moderate in 90% of the cases and as severe in 9% of the cases. Information about severity was missing for 1% of the bleeds.

The most frequent location of the bleeds was in a joint, which accounted for 75% of the bleeds and 65% of the total number of the bleeds were in a target joint.

Haemostatic response

The haemostatic response after treatment of a bleed with turoctocog alfa was evaluated on a 4-point scale as excellent, good, moderate or none. The haemostatic response was rated as excellent for 140 (28%) of the bleeds, good for 263 (53%) of the bleeds, moderate for 62 (12%) of the bleeds, and none for 12 (2.4%) of the bleeds. For the remaining 22 (4%) of the bleeds, the haemostatic response was not rated.

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. It should be noted that only 1 infusion was reported for treatment of 82% of the bleeds with missing haemostatic responses, suggesting that this proportion of the bleeds with missing haemostatic responses was successfully treated with turoctocog alfa. It should also be noted that in 10% of the bleeds the haemostatic response was rated as excellent even though more than 1 infusion was used to stop the bleed.

Number of infusions of turoctocog alfa used for treatment of bleeds

Of the 499 reported bleeds, 357 (71.5%) were stopped with 1 infusion of turoctocog alfa and 89 (17.8%) were stopped with 2 infusions. Thus, 89.4% of the bleeds were stopped with one or two infusions of turoctocog alfa. One patient (patient number 183101) reported 26 infusions to stop a muscle bleed caused by a trauma. The duration of the bleed was 304 hours and the haemostatic response was rated as 'good'.

Some patients continued to take turoctocog alfa after they had reported the bleed as being stopped in order to prevent re-bleeding. When looking at the number of infusions from the start of the bleed until the prevention was resumed, 1 infusion was required for 313 (62.7%) bleeds and 2 infusions were required for 102 (20.4%) bleeds. The mean number of infusions required from start to stop of a bleed was 1.5 infusions/bleed and the median number of infusions was 1 infusion/bleed.

Time to control of a bleed

The mean duration from start to stop of a bleed was 16.4 hours ranging from 15 minutes to 304 hours. The mean time from start of a bleed and until the first administration of turoctocog alfa was 2.83 hours ranging from 0 to 56 hours and the mean time from the first administration of turoctocog alfa and until the bleed stopped was 13.6 hours ranging from 0 to 300 hours.

Adolescents

There were no apparent differences observed in the adolescent population in the analyses of bleeds and the same patterns and trends were seen as described above for the total population. However, the success rate for treatment of bleeds in the adolescent population was 71.6% which was approximately 10% lower than for the total population.

Efficacy of turoctocog alfa when used in surgery

A total of 9 surgeries in 9 patients were performed during the trial. Eight of these were major surgeries and 1 was a minor surgery. Only one of the surgeries was done in an adolescent patient. The surgery indications included arthropathy and chronic pain in left knee for 1 patient, synovialitis for 1 patient, semi-impacted tooth and removal of tooth root for 1 patient, arthropathy for 4 patients, religious (circumcision) for 1 patient and recurrent haemarthosis for 1 patient.

In addition, 3 'other surgical procedures' were performed in 3 patients and 2 were related to tooth extractions and one was a removal of a periumbilicial abscess.

Haemostatic response during and after surgery

Haemostasis was successful in all the surgeries and no treatment failures were reported. The haemostatic response during surgery was rated excellent in 78% of the surgeries and the haemostatic response when haemostasis had been achieved was rated excellent in 67% of the cases.

No wound haematomas were reported at any time for any of the patients undergoing surgery.

Table 24: Haemostatic response by type of surgery – full analysis set

	Major Surgery	Minor Surgery	Total Part C
Number of patients	8	1	9
Number of surgeries	8 (100.0)	1 (100.0)	9 (100.0)
Haemostatic response during surgery			
Excellent	6 (75.0)	1 (100.0)	7 (77.8)
Good	2 (25.0)	0 (0.0)	2 (22.2)
Moderate	0 (0.0)	0 (0.0)	0 (0.0)
None	0 (0.0)	0 (0.0)	0 (0.0)
Haemostatic response when haemostasis has been achieved			
Excellent	5 (62.5)	1 (100.0)	6 (66.7)
Good	3 (37.5)	0 (0.0)	3 (33.3)
Moderate	0 (0.0)	0 (0.0)	0 (0.0)
None	0 (0.0)	0 (0.0)	0 (0.0)

Consumption of turoctocog alfa during and after surgery

During the entire surgery period, the mean consumption of turoctocog alfa was 831 IU/kg per surgery ranging from 331 to 1468 IU/kg. From Day 1 to Day 7 of the surgery, the mean consumption was 432 IU/kg per surgery and from Day 8 and until the patients returned to the preventive regimen, the mean consumption was 399 IU/kg per surgery.

Blood loss during and after surgery

The actual mean blood loss during surgery was 258 mL per surgery.

Haemoglobin level before, during and after surgery

The mean haemoglobin level before surgery was 9.53 mmol/L ranging from 8.32 to 10.35 mmol/L. The mean haemoglobin levels 1 hour and 24 hours after surgery were 9.4% and 16.2% lower, respectively.

Blood product transfusion during and after surgery

One blood product transfusion of 3 units of red blood cells was reported for one patient.

Ancillary analyses

Table 25: Treatment of bleeds; success by other factors – all patients – full analysis set

Factor	N	Percentage of treatment successes
Compliance with preventive treatment		
Good compliance	440	83.9
Less compliance	59	57.6
Location of bleed		
Joint	373	80.4
Target joint[a]	325	81.5
Subcutaneous	13	69.2
Muscular	25	88.2
Gastrointestinal	3	66.7
Cause of bleed		
Spontaneous	332	79.8
Traumatic	124	83.1
Other		89.2
Time from start of bleed until the first infusion of turoctocog alfa		
<2 hours	302	82.2
2-4 hours	84	80.9
>4 hours	91	79.1
Time of bleed		
7 a.m. to 11 a.m.	135	80.0
11 a.m. to 3 p.m.	92	78.3
3 p.m. to 7 p.m.	88	78.4
7 p.m. to 11 p.m.	85	89.4
11 p.m. to 3 a.m.	34	73.5

Patient-reported Outcomes

The EQ-5D had 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, 3 answers were available. In the 'mobility' and 'pain/discomfort' domains, most of the patients reported some problems with mobility and moderate pain both at baseline and at the end of trial, probably as a consequence of their haemophilia. In the three other domains, most of the patients had no problems at baseline and at end of trial.

In addition to the domains, EQ-5D has a VAS scale ranging from 0-100 intended for the patients to report their health state today. The mean change in the VAS scale from baseline to the end of trial was a modest improvement of 2.5 points. However, some patients had substantial changes in the VAS scale ranging from a worsening of 70 points to an improvement of 67 points. A total summary score for EQ-5D was calculated for each patient at baseline and at end of trial. The mean total summary score at baseline was 0.725 ranging from -0.181 to 1.000. The mean change from baseline to end of trial in the total summary score was modest (0.008).

The patients who underwent surgery also completed the PRO questionnaires on the pre-surgery day and again on the day where they returned to their preventive treatment. The mean change on the

EQ-5D VAS scale over this period was an improvement of 11.1 points ranging from a worsening of 2 points to an improvement of 30 points. The mean change from the pre-surgery day to return on preventive treatment in the EQ-5D total summary score was modest (0.041).

No noteworthy change was observed from baseline to end of trial in total HAEM-A-QOL score for adults.

Study NN7008-3545 A multi-centre, open-label, non-controlled trial on safety and efficacy of turoctocog alfa in previously treated paediatric patients with haemophilia A.

Methods

Study Participants

Main inclusion criteria:

- Informed consent obtained before any trial-related activities. (Trial-related activities are any procedure that would not have been performed during normal management of the patient).
- Male patients with severe (FVIII ≤ 1%) haemophilia A. *This inclusion criterion was clarified with Amendment no. 2: (baseline FVIII ≤ 1%) was corrected to (FVIII ≤ 1%).*
- Age <12 years and weight ≥ 11 kg.
- Documented history of a minimum 50 exposure days to FVIII products (prophylaxis / prevention / surgery / on-demand).
- No FVIII inhibitors (≥ 0.6 BU) at screening.
- Documented negative FVIII inhibitor test(s) or documented FVIII recovery tests (within expected normal ranges) within first 50 exposure days. *This inclusion criterion was changed with Amendment no. 2: a cut-off value of 0.6 BU was deleted since the historical laboratory cut-off value for inhibitor testing in some participating countries was 1 BU.*
- Immunocompetent, defined as either HIV negative or if HIV positive, CD4+ >200 cells/µLaccording to medical records.

Main exclusion criteria:

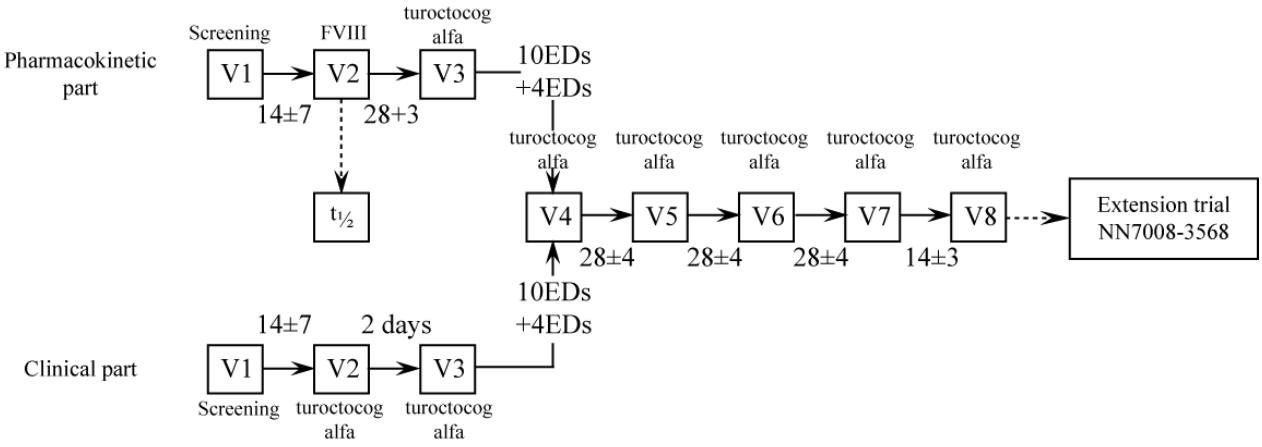
- Known or suspected allergy to hamster protein or intolerance to trial product or related products.
- Previous participation in this trial defined as withdrawal after administration of trial product.
- Any history of FVIII inhibitors. *This exclusion criterion was changed with Amendment no. 2: a cut-off value of 0.6 BU was deleted since the historical laboratory cut-off value for inhibitor testing in some participating countries was 1 BU.*
- Surgery planned to occur during the trial (exceptions are port placement, dental extractions, and minor, uncomplicated emergent procedures).
- Platelet count <50,000 platelets/µL.

- Congenital or acquired coagulation disorders other than haemophilia A.
- Ongoing treatment or planned treatment during the trial with chemotherapy, immunomodulatory agents (e.g. intravenous immunoglobulin (IVIG), routine systemic corticosteroids).
- The receipt of any investigational product within 30 days prior to inclusion in this trial *(The following was added by Amendment no. 1: For Brazil, only: The receipt of any investigational drug within one year prior to screening for this trial (i.e. Visit 1), unless there, at the investigator's discretion, is a direct benefit to the research subject. In order for Novo Nordisk to be able to report those subjects having received investigational products 1-12 months prior to entering the NN7008-3545 trial, Novo Nordisk will on an ongoing basis collect this information and document it in their monitoring reports. In addition to this the information will be available from the progress reports sent to ethics committees).*
- Any disease or condition which, judged by the investigator, could imply a potential hazard to the patient, interfere with the trial participation or trial outcome.
- Renal dysfunction defined as serum creatinine level ≥ 2 times upper limit of normal or glomerular filtration rate decrease > 50%.
- Liver dysfunction defined as alanine aminotransferase (ALT) or gamma-glutamyl transferase ≥ 2 times upper limit of normal, or jaundice.
- Documented diagnosis of obesity (only for patients in the pharmacokinetic part) defined as weight equal to or greater than the 95th percentile for age.
- Unwillingness, language or other barriers precluding adequate understanding and/or cooperation from parents and child.

Treatments

The trial comprised eight scheduled visits. All patients attended a screening visit (Visit 1) in order to assess their eligibility. In the pharmacokinetic part of the trial, pharmacokinetic sessions were performed at Visit 2 and Visit 3. Preventive treatment with turoctocog alfa was administered to these patients from Visit 4 to Visit 8 (clinical part of trial). For patients in the clinical part of the trial, the preventive treatment started at Visit 2 and continued until Visit 8. Preventive treatment continued until each patient reached at least 50 exposure days with turoctocog alfa.

If the patient/parents/LAR's wished to continue treatment with turoctocog alfa the end-of-trial visit would also be the first visit in the extension trial NN7008-3568.



Preventive treatment:

During the clinical part of this trial the patients received bleeding preventive treatment with a single dose of turoctocog alfa of 25-50 IU/kg every second day or 25-60 IU/kg three times weekly. The trial product was preferably administered in the morning and was administered as a slow bolus i.v. injection (approximately 1-2 mL/min).

The duration of treatment from first to last turoctocog alfa administration was approximately 18-22 weeks corresponding to at least 50 exposure days.

Treatment of bleeds:
Dose level for treatment of bleeds was determined according to the following formula: Required units = body weight (bw) (kg) x desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL). The dose for treatment of bleeds was aimed to achieve an expected post-injection level of at least 0.50 IU/mL of turoctocog alfa. Higher doses up to a total dose of 150 IU/kg per day could be used at the investigator's discretion based on the site and severity of the bleed, and the clinical situation. When the bleed had resolved, the patient could resume the preventive regimen.

Objectives

The primary objective: to evaluate safety of turoctocog alfa in paediatric previously treated patients <12 years of age with haemophilia A.

The secondary objectives: to evaluate pharmacokinetics of turoctocog alfa in paediatric previously treated patients <12 years of age with haemophilia A, to evaluate efficacy of turoctocog alfa in paediatric previously treated patients <12 years of age with haemophilia A and to assess and compare patient-reported outcomes from baseline to end of trial in paediatric previously treated patients <12 years of age with haemophilia A.

Outcomes/endpoints

The efficacy endpoints were as follows:

- Bleeding prevention
    - Total consumption of turoctocog alfa per patient (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 month.
- 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

No formal sample size calculations were performed. The sample size was based on the guideline EMA/CHMP/BPWP/144533/2009.

Randomisation

There was no randomisation of patients as the study was a single arm study.

Blinding (masking)

There was no blinding of patients as the study was an open-label study.

Statistical methods

There was no statistical analysis plan.

Bleeding prevention:

The annualised bleeding rate was estimated using a Poisson model allowing for overdispersion. For all patients, including withdrawn patients, 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 annualised bleeding rate.

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

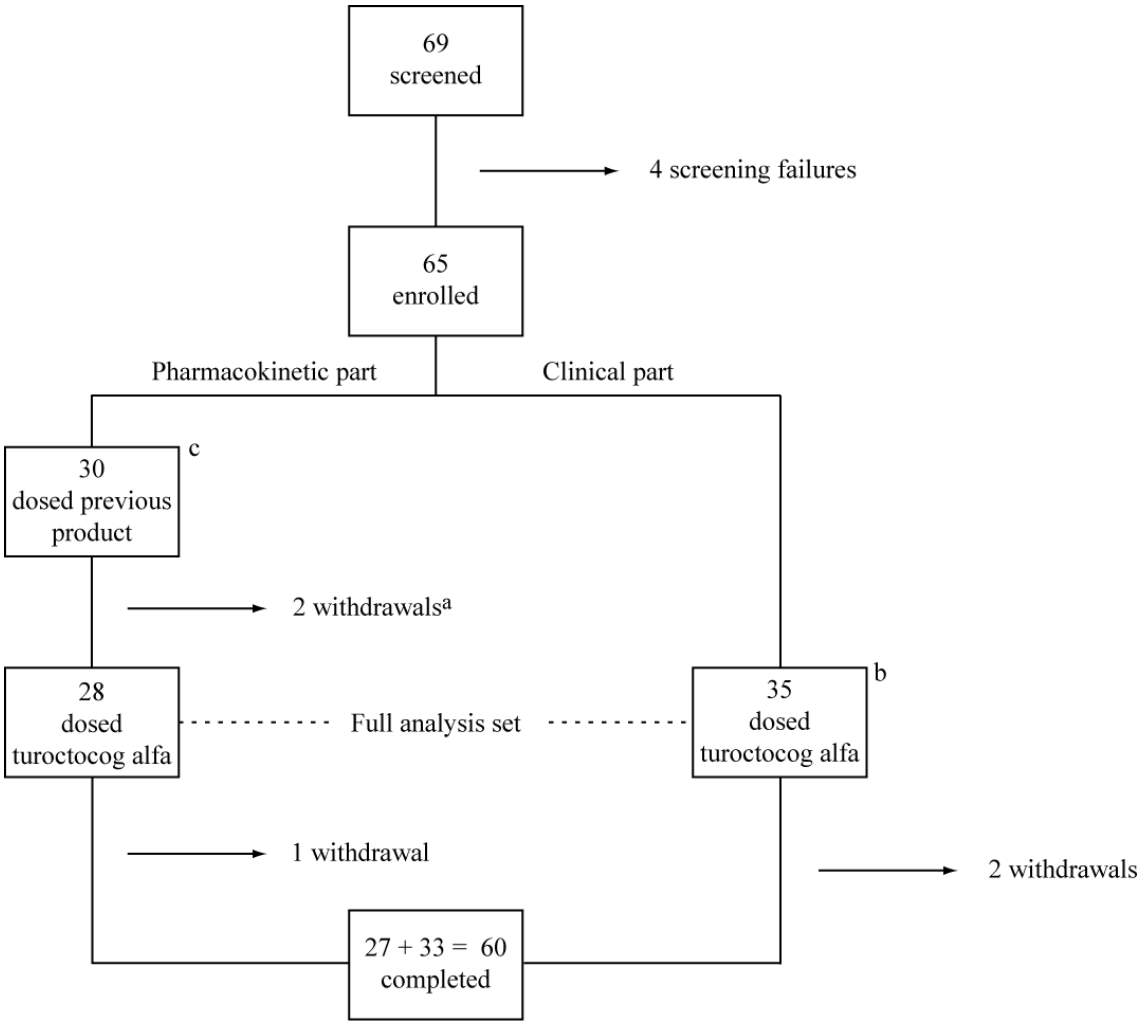
or none, the treatment was counted as a failure. As a conservative approach, the missing ratings were included as treatment failures.

All other endpoints have been analysed in a descriptive manner.

Results

Participant flow

Table 26: Patients disposition



Recruitment

In this multi-centre trial, 26 study sites enrolled and dosed at least one patient. The country distribution was as follows (number of actively recruiting sites per country in parenthesis): Brazil (3), Italy (1), Lithuania (1), Macedonia (1), Malaysia (1), Poland (2), Russia (2), Serbia (1), Taiwan (1), Turkey (3) and the US (10).

The trial was initiated in June 2010 (first patient first visit) and completed in November 2011 (last patient last visit).

Conduct of the study

During the conduct of the study there were 5 substantial amendments to the protocol.

Baseline data

The population was equally split between the two age cohorts (31 small children [0 - <6 years] and 32 older children [6 - <12 years]) and consisted of males with severe haemophilia (FVIII activity ≤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 patients were White (84%) and the second-largest group was Asian (10%). Nineteen percent (19%) of the patients were from the US, 14% were from Brazil, 13% were from Russia and 11% were from Turkey, while the remaining 42% of the patients were distributed between the other 7 countries.

A total of 54 patients (24 small children and 35 older children) had information on their FVIII genotype; the most frequent mutations were inversions and substitutions.

Numbers analysed

A total of 69 patients were screened for this trial and 65 patients were enrolled. Of the 65 enrolled patients, 2 patients were withdrawn before dosing with turoctocog alfa (due to a historical positive inhibitor test and due to difficulties in attending the planned visits) and 3 patients were withdrawn after dosing (due to treatment with another FVIII product than turoctocog alfa, due to non-compliance with the trial procedures and for one patient it was decided that he should not continue in the trial); thus 60 patients completed the trial. Of the 60 patients completing the trial, 29 were small children (0 - < 6 years) and 31 were older children (6 - < 12 years). Of the 63 dosed patients, 28 (14 in each age cohort) were dosed in the pharmacokinetic part of the trial while the remaining 35 (17 small children and 18 older children) were dosed in the clinical part of the trial.

All 63 patients who were dosed with turoctocog alfa were included in the full analysis set (FAS) on which all the efficacy analyses, including analyses of patient-reported outcomes, are based.

Outcomes and estimation

A total of 126 bleeds were treated during the trial. A total of 22 patients (35%) did not experience any bleeds during the trial. The number of patients experiencing a specific number of bleeds during the trial is presented in the following table.

Table 27: Frequency of bleeds - FAS

	Frequency of Bleeding
Number of patients, N	63
Number of Bleeds, N* (%)	
0	22 (34.92)
1	11 (17.46)
2	12 (19.05)
3	5 (7.94)
4	6 (9.52)
5	1 (1.59)
6	3 (4.76)
7	1 (1.59)
9	1 (1.59)
13	1 (1.59)

* Number of patients

The majority of the bleeds (67%) were caused by a trauma, 32% were spontaneous and for the remaining 1%, the cause was not reported in the diary. The proportion of bleeds caused by trauma was 83% among the small children and 55% among the older children. The bleeds were classified as mild/moderate in 91% of the cases, as severe in 6% of the cases and for the remaining 3%, the classification was not reported in the diary. Joints were the most frequent locations of bleeds, accounting for 47% of which 22% were also in a target joint. The most frequently reported start time of a bleed was from 7 p.m. to 11 p.m. and the least frequent was from 11 p.m. to 3 a.m. Two (2) of the 126 bleeds were categorised as re-bleeds. Apart from the higher frequency of traumatic bleeds in small children compared to older children, there were no noteworthy differences between the two age groups.

Consumption of turoctocog alfa

Bleeding prevention

The mean total consumption per month per patient for prevention and treatment of bleeds was 487 IU/kg/patient ranging from 286 to 765 IU/kg/patient and slightly higher for patients in good compliance than for patients who were less compliant.
The mean total consumption per year for prevention and treatment of bleeds was 5974.1 IU/kg/patient ranging from 3542 to 9532 IU/kg/patient.
The mean total consumption for prevention, treatment of bleeds, minor surgery and pharmacokinetic sessions during the entire trial period was 2251 IU/kg/patient ranging from 830 to 5076 IU/kg/patient. There were no noteworthy differences between the small children and the older children.

A total of 3610 preventive doses of turoctocog alfa were taken during the trial and the mean preventive dose was 36.8 IU/kg ranging from 3.2 to 73.9 IU/kg.
The mean consumption per month for prevention was 462 IU/kg/month and for patients in good compliance it was 469 IU/kg/month, while for patients who were less compliant it was 426 IU/kg/month.
The same pattern was seen with the yearly consumption where the overall mean was 5641 IU/kg/year, 5736 IU/kg/year for patients in good compliance and 5073 IU/kg/year for patients who were less compliant.
There were no noteworthy differences between the small children and the older children.

Treatment of bleeds

A total of 187 doses were taken during the trial for treatment of 126 bleeds and the mean dose for treatment of a bleed (from start to stop of the bleed) was 40.4 IU/kg/dose ranging from 25.5 to 193.8 IU/kg/dose. The mean consumption used for treatment of bleeds (from start to stop of the bleed) was 54.2 IU/kg/bleed. The reason that the mean dose for treatment of a bleed was lower than the mean consumption from start to stop of a bleed was that some bleeds were treated with more than one dose. The mean consumption from the time the bleed stopped until the patient returned to preventive regimen was 8.0 IU/kg/bleed. The consumption of turoctocog alfa used for treatment of bleeds from start to stop of bleed was lower for patients in good compliance than for less compliant patients (48.9 vs. 94.2 IU/kg/bleed).
The mean dose for treatment of a bleed was slightly higher for small children than for older children (45.5 vs. 37.6 IU/kg/dose). Apart from this, there were no noteworthy differences between the small children and the older children.

Estimated annualised bleeding rates

The overall estimated annualised bleeding rate was 5.33 bleeds/patient/year (95% CI: 3.90-7.28 bleeds/patient/year) and for young children (0-<6 years) it was 4.73 bleeds/patient/year (95% CI: 3.06-7.30 bleeds/patient/year) while for older children (6 - <12 years) it was 5.86 bleeds/patient/year (95% CI: 3.76-9.13 bleeds/patient/year).

Haemostatic response

The haemostatic response was rated as excellent for 68 (54%) of the bleeds, good for 48 (38%) of the bleeds, moderate for 5 (4%) of the bleeds, and none for 2 (1.6%) of the bleeds. For the remaining 3 (2.4%) bleeds, the haemostatic response was not rated.
One of the bleeds where the haemostatic response was 'none' was a mild/moderate traumatic mucosal bleed. The duration of the bleed was 22 hours and required 2 infusions from start to stop of the bleed. The other bleed where the haemostatic response was 'none' was for patient number 866501 and is described in more detail in the following table.

Table 28: Description of response in patient where haemostatic response was recorded as "none"

			Number of infusions						
Patient number	Age (years)	Duration of bleed (hours)	Start to stop of bleed	Start of bleed to prevention was resumed	Cause of the bleed	Site of the bleed	Other therapy used	Classification of the bleed	Haemostatic response
866501	7	213*	8	8	Traumatic	Left hand bleed, middle and ring finger, knot in palm of hand	-	-	None
		-	5	5	-	Haemarthrosis	Compression	-	-

* As time at stop of bleed was not reported, 23:59 was used for calculating the duration

If the haemostatic response was rated as excellent or good, the treatment of the bleed was considered a success. If the haemostatic response was rated as moderate or none, the treatment was considered a failure. 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. It should be noted that only 1 or 2 infusions were reported for treatment of 2 of the 3 bleeds with missing haemostatic responses, while the last bleed with missing haemostatic response required 5 turoctocog alfa infusions. Furthermore, for 5 of the bleeds, the haemostatic response was rated as excellent even though more than 1 infusion was used to stop the bleed. There were no noteworthy differences in haemostatic response between the two age groups.

Number of infusions of turoctocog alfa used for treatment of bleeds

Of the 126 reported bleeds, 102 (81.0%) were stopped with 1 infusion of turoctocog alfa and 18 (14.3%) were stopped with 2 infusions. Details on bleeds that required more than 2 infusions are presented in the following table.

Table 29: Description of events where patients required more than 2 infusions to treat a bleed

			Number of infusions						
Patient number	Age (years)	Duration of bleed (hours)	Start to stop of bleed	Start of bleed to prevention was resumed	Cause of the bleed	Site of the bleed	Other therapy used	Classification of the bleed	Haemostatic response
121504	4	75	6	6	Traumatic	Back pain (scapula region)	Compression	Severe	Good
381503	9	19	3	3	Traumatic	Haemarthrosis	Compression	Mild/moderate	Excellent
703501	11	-	6	6	Traumatic	Left ankle	Compression	Mild/moderate	Good
		48	4	4	Traumatic	Subcutaneous	Other	Severe	Good
866501	7	213*	8	8	Traumatic	Left hand bleed, middle and ring finger, knot in palm of hand	-	-	None
		-	5	5	-	Haemarthrosis	Compression	-	-

* As time at stop of bleed was not reported, 23:59 was used for calculating the duration

Some patients continued to take turoctocog alfa after they had reported the bleed as being stopped in order to maintain haemostasis. When looking at the number of infusions from the start of the bleed until the prevention was resumed, 1 infusion was required for 94 (74.6%) bleeds and 2 infusions were required for 17 (13.5%) bleeds. The mean number of infusions required from start to stop of a bleed was 1.3 infusions/bleed and the median number of infusions was 1 infusion/bleed.

Time to control of a bleed

The mean duration from start to stop of a bleed was 8.88 hours ranging from 0.17 to 53.5 hours. The mean time from start of a bleed and until the first administration of turoctocog alfa was 1.68 hours ranging from 0 to 16.8 hours and the mean time from the first administration of turoctocog alfa and

until the bleed stopped was 7.5 hours ranging from 0 to 53.5 hours. The same pattern was observed when looking separately at the small children and older children.

Ancillary analyses

Efficacy of turoctocog alfa when used in surgery

Two (2) minor surgeries in 2 patients were performed during the trial. One surgery in patient number 705501 was a dental extraction and the other in patient number 865501 was described as 'minor uncomplicated surgery' covering removal of a central venous access port. Haemostasis was rated as excellent on both surgeries. The patient who had a dental extraction received a pre-surgery dose of turoctocog alfa of 50 IU/kg and after the surgery he had tranexamic acid 500 mg two times daily for 3 days during the recovery period. The other patient had a presurgery dose of turoctocog alfa of 100 IU/kg and a single dose of 50 IU/kg during the post-surgical recovery period.

Patient-reported outcome

Patient-reported outcomes were measured at Visit 1 and Visit 8 in order to investigate the change from baseline to the end-of-trial. The HAEMO-QOL questionnaire was available for two age groups (4-7 years and 8-12 years of age) in a patient version and in a parent version. The biggest change in the mean total summary score was seen in the parents' versions for patients who were treated on-demand prior to trial entry (an improvement of 10.42 points for 4-7 year old patients and an improvement of 14.30 points for 8-12 year old patients). Apart from this, no noteworthy changes were observed from baseline to end of trial in the total HAEMO-QOL scores.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 30: Summary of Efficacy for trials

Title: **A multi-centre, open-label, non-controlled trial on safety and efficacy of turoctocog alfa in previously treated paediatric patients with haemophilia A.**			
Study identifier	**Study NN7008-3545**		
Design	The trial comprised a pharmacokinetic part and a clinical part. Patients not involved in the pharmacokinetic sessions could start directly on preventive treatment in the clinical part of the trial. Preventive treatment continued until each patient reached at least 50 exposure days with turoctocog alfa. An exposure day was defined as any day that the patient had been exposed to turoctocog alfa for prevention of bleeds, for treatment of bleeds and during the pharmacokinetic sessions.		
	Duration of main phase:	Initiation date: 18 June 2010 (first patient first visit) Completion date: 21 November 2011 (last patient last visit)	
Treatments groups	turoctoco alfa	Single arm trial	
Endpoints and definitions	<Co->Primary endpoint	Bleeding prevention	• Total consumption of turoctocog alfa per patient (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 month.
	<Secondary> <other: specify> endpoint	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.
Database lock	13 December 2011, updated 1 February 2012		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set			
Descriptive statistics and estimate variability	Treatment group	Turoctocog alfa		
	Number of subject	63		
	Annualised bleeding rate	The overall estimated annualised bleeding rate was 5.33 bleeds/patient/year (95% CI: 3.90-7.28 bleeds/patient/year) and for young children (0-<6 years) it was 4.73 bleeds/patient/year (95% CI: 3.06-7.30 bleeds/patient/year) while for older children (6 - <12 years) it was 5.86 bleeds/patient/year (95% CI: 3.76-9.13 bleeds/patient/year).		

	Haemostatic response	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.
	Number of infusions needed to stop a bleeding	Of the 126 reported bleeds, 102 (81.0%) were stopped with 1 infusion of turoctocog alfa and 18 (14.3%) were stopped with 2 infusions.
	FVIII consumption	The mean preventive dose was 36.8 IU/kg ranging from 3.2 to 73.9 IU/kg. The mean consumption per month for prevention was 462 IU/kg/month and the mean yearly consumption was 5641 IU/kg/year. The mean dose for treatment of a bleed (from start to stop of the bleed) was 40.4 IU/kg/dose ranging from 25.5 to 193.8 IU/kg/dose. The mean consumption used for treatment of bleeds (from start to stop of the bleed) was 54.2 IU/kg/bleed.
	Haemostatic response during surgery	Two (2) minor surgeries in 2 patients were performed during the trial. Haemostasis was rated as excellent on both surgeries.

<table>
<tr><td colspan="4">Title: A multi-centre, open-label, non-controlled trial on safety and efficacy of turoctocog alfa in prevention and treatment of bleeds in previously treated patients with haemophilia A

Sub-trial: Safety and efficacy of turoctocog alfa in prevention and treatment of bleeding during surgical procedures in patients with haemophilia A</td></tr>
<tr><td>Study identifier</td><td colspan="3">Study NN7008-3543</td></tr>
<tr><td>Design</td><td colspan="3"><u>Part A:</u> Included the patients who completed the pharmacokinetic trial (Trial 3522).

<u>Part B:</u> Included patients who had not previously participated in the pharmacokinetic trial (Trial 3522). Part B was initiated when 20 patients in part A had a safety assessment based upon results from Trial 3522.

<u>Surgery sub-trial:</u> Included any of the patients from part A and part B that, during the course of the trial, needed to undergo a major or minor surgical procedure requiring at least 7 days of daily FVIII treatment, including the day of surgery. In the peri-operative period, turoctocog alfa should be administered as bolus infusions.

Patients eligible for part A or part B of the trial received turoctocog alfa for prevention of bleeds for at least 75 preventive exposure days. Prevention and treatment of bleeds was carried out at home with intravenous (i.v.) injections by the patient or a support person. Details on home treatment were registered in a diary by the patient.</td></tr>
<tr><td></td><td colspan="2">Duration of main phase:</td><td>Initiation date: 7 April 2009 (first patient first visit)
Completion date: 21 September 2011 (last patient last visit)</td></tr>
<tr><td>Hypothesis</td><td colspan="3"></td></tr>
<tr><td>Treatments groups</td><td colspan="2">turoctoco alfa</td><td>Single arm trial</td></tr>
<tr><td></td><td colspan="3"></td></tr>
<tr><td>Endpoints and definitions</td><td>Primary endpoint
Part A and B</td><td>The incidence rate of FVIII inhibitors (⩾ 0.6 BU)</td><td></td></tr>
<tr><td></td><td>Secondary endpoint
Part A and B</td><td>Bleeding prevention</td><td>• Total consumption of turoctocog alfa per patient (prevention and treatment of bleeds) per month
• Actual consumption of turoctocog alfa (IU/kg /month) for prevention
• Average number of bleeds per month</td></tr>
</table>

		Treatment of bleeds	• Haemostatic effect of turoctocog alfa evaluated according to a predefined four grade scale: None, moderate, good or excellent. • The 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)
	Secondary endpoint Part C	Haemostatic effect	• Haemostatic effect of turoctocog alfa assessed by evaluation according to a predefined four point scale: None, moderate, good or excellent. If the haemostatic response was rated as excellent or good, the treatment of the bleed was considered a success. If the haemostatic response was rated as moderate or none, the treatment was considered a failure.
		Actual consumption	• 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 blood loss	• Comparison of actual and anticipated blood loss
		Haemoglobin level	• Haemoglobin level prior to surgery, during, and after surgery (pre-operative, intra-operative, and post-operative)
		Blood product transfusion	• Number of blood transfusion to attain haemostasis
	Patient-reported outcomes		Several questionnaires were used to assess disease and age-group specific quality of life (QOL) and treatment satisfaction: age specific versions of HAEMO-QOL HEMO-SAT, EQ-5D (European Quality of Life - 5 Dimensions) were used.
Database lock	18 October 2011, updated 20 December 2011		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set			
Descriptive statistics and estimate variability	Treatment group	Turoctocog alfa		
	Number of subject	150		
	Annualised bleeding rate	The total **estimated mean bleeding rate** was **5.55** bleeds/patient/year for **adolescents** and **6.68** bleeds/patient/year for **adults**. The total **median bleeding rate** was **3.66** bleeds/patient/year.		
	Haemostatic response	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.		
	Number of infusions needed to stop a bleeding	Of the 499 reported bleeds, **357 (71.5%)** were stopped with 1 infusion of turoctocog alfa and **89 (17.8%)** were stopped with 2 infusions. Thus, 89.4% of the bleeds were stopped with one or two infusions of turoctocog alfa.		
	FVIII consumption	The **mean preventive dose** was **24.4** IU/kg ranging from 12.8 to 97.4 U/kg. The mean **consumption** per month for **prevention** was **309** IU/kg/month. The mean **yearly consumption for prevention** was **3812** IU/kg/year. A total of 813 doses were taken during the trial for treatment of 499 bleeds and the **mean dose for treatment** of a bleed was **30.4** IU/kg/dose. The mean **consumption** used for **treatment of bleeds** (from start to stop of the bleed) was 45.6 IU/kg/bleed.		

	Haemostatic response during surgery	A total of 9 surgeries in 9 patients were performed during the trial. Eight of these were major surgeries and 1 was a minor surgery. Haemostasis was successful in all the surgeries and no treatment failures were reported. The haemostatic response during surgery was rated **excellent** in **78%** of the surgeries.

Supportive study

Study NN7008-3568: Safety and efficacy of turoctocog alfa in prevention and on-demand treatment of bleeding episodes in patients with haemophilia A
Sub-trial: Efficacy and safety of turoctocog alfa in prevention and treatment of bleeding during surgical procedures in patients with haemophilia A
Interim analysis including data in the clinical database as of 21 November 2011

Methods
The trial was designed as an extension trial for patients completing one of the trials NN7008–3543, NN7008-3545, NN7008-3600 or NN7008-3893. The trial was an open-label, multi-centre, multi-national, single-arm trial investigating long-term safety and efficacy of turoctocog alfa in patients with severe haemophilia A without inhibitors. 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.

Study Participants
Inclusion criteria

- Informed consent obtained before any trial-related activities. (Trial-related activities are any procedure that would not have been performed during normal management of the patient).
- Completion of the pivotal trial (NN7008-3543) or paediatric trial (NN7008-3545) or Japanese trial (NN7008-3600) or pharmacokinetic trial (NN7008-3893).

Exclusion criteria

- Previous participation in the current trial (defined as withdrawal) or withdrawn patients from NN7008-3522, NN7008-3543, NN7008-3545, NN7008-3600 or NN7008-3893 after administration of trial product, unless the previous trial protocol declared that the patient was allowed to be transferred to NN7008-3568 trial.

Eligibility criteria for patients undergoing surgery

- Documented history of at least 150 exposure days to any FVIII concentrates (preventive or on-demand regimen).
- Patients requiring major or minor surgical procedures.

Treatments

Subjects were treated either in the preventive regimen or in the on-demand regimen. Switching regimens (i.e. from preventive to on-demand or from on-demand to preventive) during the trial was permitted at an assessment visit, surgery visit, dispensing visit or unscheduled visit.

Treatment in the different regimens and during surgery is summarised in the following table.

Treatment[a]	Dose (IU/kg)	Frequency	FVIII level[b]
Preventive	20-50	Once every second day	Trough ≥0.01 IU/mL or LOD
Preventive	20-60	3 times weekly	Trough ≥0.01 IU/mL or LOD
Treatment of bleeds	20-200[c]	Investigator's discretion	Recovery ≥0.5 IU/mL
Pharmacokinetic dosing[d]	50 ± 5	Once	NA
Surgery Day 1	20-200[c]	Investigator's discretion	Trough or FVIII level >0.5 IU/mL
Surgery: Day 2-7	20-200[c]	Investigator's discretion	Trough or FVIII level >0.5 IU/mL
Surgery: Day 8-last day of the post-surgery recovery period	20-200[c]	Investigator's discretion	Local guidelines

LOD: Limit of detection

[a] The patient was only dosed with one of these treatments at a time

[b] Dose adjustment was based on the trough level (or FVIII level in case of continuous infusion regimen in surgery) and an assessment of the clinical efficacy in the individual patient (i.e. bleeds)

[c] The daily dose must not exceed 200 IU/kg.

[d] Pharmacokinetic dosing was performed before continuous infusion in surgery only.

Objectives

The primary objective: to assess the safety of turoctocog alfa for prevention and treatment of bleeds.
The secondary objective: to assess the efficacy of turoctocog alfa for prevention and treatment of bleeds.

Objectives for the sub-trial in surgery

The primary objective was to evaluate the efficacy of turoctocog alfa in surgery.
The secondary objectives were to evaluate the safety of turoctocog alfa in surgery and, with amendment 1 this objective was added, to evaluate the haemostatic response to turoctocog alfa in the post-surgery period.

Outcomes/endpoints

The efficacy endpoints were as follows:

<u>During preventive regimen</u>

- Annualised bleeding rate related to the preventive period
- Haemostatic response to turoctocog alfa (none, moderate, good or excellent) in treatment of bleeds

<u>During on-demand regimen</u>

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

Surgery sub-trial

- Haemostatic effect of turoctocog alfa assessed by evaluation according to a predefined four point scale: None, moderate, good or excellent
- 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)
- Blood product transfusion

Sample size

The sample size was based on the number of patients who completed Trials NN7008-3543, NN7008-3545, NN7008-3600 and NN7008-3893.

Randomisation

The patients were not randomised as this is a single arm trial.

Blinding (masking)

The patients were not blinded as this is an open label trial.

Statistical methods

Efficacy Endpoints

Bleeding prevention: Annualised bleeding rates were estimated using a Poisson model allowing for overdisperson and presented together with 95% confidence intervals.

In the protocol a secondary efficacy endpoint was specified specifically for the prevention period. According to the protocol the endpoint was to be 'Average number of bleeds per month reported during the prevention period'. The prevention period was specified as related to 'subject on preventive regimen'. However, as all subjects start in this trial on the preventive regimen, and as some subjects will switch to on-demand regimen, the text in the SAP has been changed to focus on 'time on preventive regimen' rather than 'subjects on preventive regimen'.

Treatment of bleeds: The haemostatic response to turoctocog alfa was evaluated according to a predefined four point scale: None, moderate, good or excellent, will be presented using counts and percentages of all treatment requiring bleeds. The haemostatic response was also evaluated according to the categories: success (good or excellent) and failure (none or moderate).

Data arising from other endpoints defined were analysed using standard descriptive measures.

Results

Participant flow

Table 31: Patient disposition

	Part A N (%)	Part C N (%)	Total (Part A and Part B) N (%)
Screened			172
Dosed	22 (100.0)	9 (100.0)	150 (100.0)
Withdrawal	0 (0.0)	0 (0.0)	4 (2.7)
Adverse Events	0 (0.0)	0 (0.0)	1 (0.7)
Initiation of Treatment with Commercial FVIII Concentrates or FVIII Containing Products Other than turoctocog alfa	0 (0.0)	0 (0.0)	1 (0.7)
Other	0 (0.0)	0 (0.0)	2 (1.3)
Lost to follow-up	0 (0.0)	0 (0.0)	1 (0.7)
Patient had a test in 2008 in other medical service which was not available at the time of enrolment with a positive inhibitor (1 BU).	0 (0.0)	0 (0.0)	1 (0.7)
Completed trial	22 (100.0)	9 (100.0)	146 (97.3)
Full analysis set*	22 (100.0)	9 (100.0)	150 (100.0)

* The full analysis set includes all dosed patient with data after dosing

Recruitment

In this multi-centre, multi-national trial the patients were enrolled at 51 sites in 18 countries: Brazil (4 sites), Croatia (2 sites), Germany (3 sites), Israel (1 site), Italy (2 sites), Japan (5 sites), Lithuania (1 site), Macedonia (1 site), Malaysia (1 site), Poland (2 sites), Russian Federation (2 sites), Republic of Serbia (5 sites), Spain (2 sites), Switzerland (1 site), Taiwan (1 site), Turkey (5 sites), the UK (1 site) and the US (12 sites).

The trial was initiated in October 2009 and is still ongoing. The submitted study report describes interim data as of the cut-off date of 21 November 2011.

Conduct of the study

Protocol amendments

Up until the cut-off date, there were 11 substantial amendments to the protocol.

A patient withdrew before dosing (reason for withdrawal: subject´s decision). For another patient no diary (and thus no dosing information) was available at the cut-off date (21 November 2011).

As of the cut-off date (21 November 2011), 8 patients had been withdrawn from the trial after dosing with turoctocog alfa. Patient one met withdrawal criterion 12 ‘Use of coagulation factors other than turoctocog alfa’ and withdrawal criterion 13 ‘Use of commercial FVIII products’ and was therefore withdrawn. Patient two was withdrawn due to an adverse event of psychotic disorder. Patient three received one dose of turoctocog alfa in the present trial and was thus included in the FAS. However, after this dose, the patient dropped out due to an adverse event at the end of his previous trial (NN7008-3543). The reason for withdrawal was listed as ‘other’. Patient four withdrew due to non-planned surgery, which logistically could not be handled within the present trial and patient five was withdrawn due to non-compliance with the protocol. The remaining 3 patients were withdrawn due to withdrawal of consent or on his own initiative.

Baseline data

The population consisted of male patients with severe haemophilia (FVIII activity ≤1%) and was divided in 4 age groups: small 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 patient entered the first turoctocog alfa trial.

Prior to the trial, the mean number of turoctocog alfa infusions per patient was 81 infusions. The majority of patients 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 patients were distributed among the other 15 countries.

Numbers analysed

A total of 189 patients were included and 187 patients were dosed with turoctocog alfa in the present trial.

Outcomes and estimation

At the cut-off date (21 November 2011), a total of 366 bleeds were reported in 86 of the 187 participating patients. It should be noted that 30 patients (16%) had not available diary data as of the cut-off date (21 November 2011), since they had not yet attended Visit 2 at which the first diary data were collected.

The majority of the bleeds (66%) were spontaneous and 34% were caused by trauma; however for the older children, 13% were spontaneous and 87% were caused by trauma. The bleeds were classified as mild/moderate in 86% of the cases and as severe in 14% of the cases. The most frequent location of the bleeds was in a joint, which accounted for 78% of the bleeds and 48% of the total number of the bleeds were in a target joint. The two most frequently reported start times of a bleed was from 7 a.m. to 11 a.m. and from 3 p.m. to 7 p.m. The least frequently reported start time was from 11 p.m. to 3 a.m.

Estimated annualized bleeding rates during preventive treatment

The overall estimated annualised bleeding rate was low (3.54 bleeds/patient/year; 95% CI: 2.90- 4.33 bleeds/patient/year) ranging from 2.61 bleeds/patient/year in adolescents to 3.71 bleeds/patient/year in adults. The estimated annualised bleeding rate for traumatic bleeds was lower than for spontaneous bleeds (1.21 vs. 2.33 bleeds/patient/year).

The estimated annualised bleeding rate for all patients varied considerably among the countries with the lowest rate in Spain (0.42 bleeds/patient/year) and the highest in the Russian Federation (9.42 bleeds/patient/year). Excluding bleeds and corresponding exposure periods that occurred more than 72 hours after the last preventive dose resulted in a decrease in the total estimated annualised bleeding rate from 3.54 to 3.10 bleeds/patient/year. Excluding bleeds and corresponding exposure periods that occurred more than 48 hours after the last preventive dose resulted in a decrease in the total estimated annualised bleeding rate from 3.54 to 2.53 bleeds/patient/year.

The mean dose used for prevention was 30.4 IU/kg ranging from 4.3 to 86.0 IU/kg.

The mean consumption per patient per year was 4898 IU/kg/patient ranging from 2041 to 9945 IU/kg/patient.

The mean consumption from start to stop of a bleed was 53.2 IU/kg/bleed ranging from 19.9 to 735.3 IU/kg/bleed.

Haemostatic response

The haemostatic response was rated as excellent for 170 (46%) of the bleeds, good for 149 (41%) of the bleeds, moderate for 44 (12%) of the bleeds, and none for 3 (1%) of the bleeds.

The 3 bleeds where the haemostatic response was rated as 'none' were:

- A mild/moderate traumatic muscular bleed, which required 4 infusions from start to stop of the bleed. The duration of the bleed was 139 hours.
- A severe spontaneous joint bleed, which required 3 infusions from start to stop of the bleed. The duration of the bleed was 47 hours.
- A severe spontaneous joint bleed, which required 5 infusions from start to stop of the bleed. The duration of the bleed was 43 hours.

If the haemostatic response was rated as excellent or good, the treatment of the bleed was considered a success. If the haemostatic response was rated as moderate or none, the treatment was considered a failure. The overall success rate for treatment of bleeds was 87.2% ranging from 73.9% in older children to 93.8% in adolescents. It should be noted that for 11 of the bleeds, the haemostatic response was rated as excellent even though more than 1 infusion was used to stop the bleed.

Number of infusions of turoctocog alfa used for treatment of bleeds

Of the 366 reported bleeds, 288 (78.7%) were stopped with 1 infusion of turoctocog alfa, 44 (12.0%) were stopped with 2 infusions and 15 (4.1%) were stopped with 3 infusions.
Details on the remaining bleeds that required more than 3 infusions are presented in the following table.

Table 32: Description of patients that required more than 3 infusions to treat a bleed

			Number of infusions						
Patient number	Age (years)	Duration of bleed (hours)	Start to stop of bleed	Start of bleed to prevention was resumed	Cause of the bleed	Site of the bleed	Other therapy used	Classification of the bleed	Haemostatic response
704104	14	28	4	4	Traumatic	Joint	-	Mild/moderate	Good
183102	22	38	4	4	Spontaneous	Joint	-	Severe	Good
861101	25	43	4	4	Traumatic	Joint	Compression	Severe	Moderate
802101	25	43	5	5	Spontaneous	Joint	-	Severe	None
853501	11	50	4	4	Traumatic	Muscular	Compression	Severe	Excellent
704104	14	54	4	4	Spontaneous	Joint	-	Mild/moderate	Moderate
551101	29	62	5	5	Spontaneous	Joint	-	Severe	Moderate
702102	18	71	8	8	Traumatic	Joint	Compression	Mild/moderate	Moderate
702101	20	96	4	4	Spontaneous	Joint	-	Mild/moderate	Moderate
281500	7	101	7	7	Traumatic	Joint	Other	Severe	Moderate
202501	8	102	4	4	Traumatic	Joint	Other	Mild/moderate	Moderate
861101	25	136	5	5	Spontaneous	Joint	-	Severe	Moderate
202003	55	137	5	5	Spontaneous	Muscular	-	Severe	Good
702101	20	139	4	4	Traumatic	Muscular	-	Mild/moderate	None
861101	21	174	8	8	Traumatic	Joint	Compression	Severe	Moderate
101003	22	240	4	4	Spontaneous	Joint	-	Severe	Moderate
181002	29	242	8	8	Traumatic	Muscular	Compression	Severe	Excellent
181103	41	273	12	12	Spontaneous	Muscular	Compression	Severe	Moderate
181001	22	646	25	25	Traumatic	Muscular	Other	Severe	Moderate

Time to control of a bleed

The median duration from start to stop of a bleed was 13.6 hours ranging from 0.17 to 273.3 hours. The median time from start of a bleed and until the first administration of turoctocog alfa was 1.0 hour ranging from 0 to 67.2 hours and the median time from the first administration of turoctocog alfa and until the bleed stopped was 10.0 hours ranging from 0.08 to 270 hours.

Efficacy of turoctocog alfa when used in surgery

Two major surgeries were performed up until the cut-off date (21 November 2011). The surgery indications were pain in left ankle and poly-trauma. Both patients received turoctocog alfa as bolus administrations during surgery.

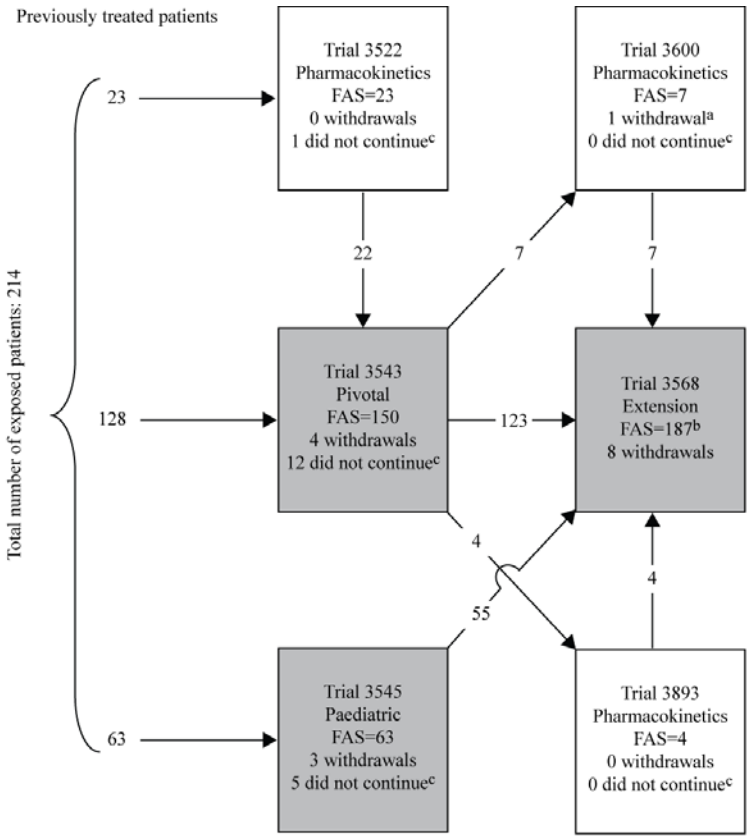
Patient with pain in left ankle
This patient was hospitalised for 7 days counting from the day of surgery and the duration of the actual surgery was 40 minutes. The consumption of turoctocog alfa during the 7 days was 192 IU/kg. No blood product transfusions, no blood loss and no wound haematoma were reported. The haemostatic response both during and after surgery was rated as excellent. The difference in haemoglobin level from pre-surgery to 1 hour post-surgery was -13.7% and from pre-surgery to 24 hours post-surgery it was -3.6%.

Patientwith poly-trauma
This surgery was linked to a serious adverse event (fall) which involved femur fracture and hand fracture. In the description of the surgery in the eCRF, the investigator had reported a 'left hip arthroprothesis and finger fracture reduction'. The patient was hospitalised for 7 days counting from the day of surgery and the duration of the actual surgery was 3 hours and 25 minutes. The consumption of turoctocog alfa during the 7 days was 278 IU/kg. The actual blood loss during the procedure was 500 mL and 2 units (538 mL) of red blood cells were transfused. No wound haematoma was reported. The haemostatic response during surgery was rated as good and the haemostatic response after surgery was rated as excellent. The difference in haemoglobin level from pre-surgery to 1 hour post-surgery was -30.9% and from pre-surgery to 24 hours post-surgery it was -16.1%.

Analysis performed across trials (pooled analyses)
Trial population

As of the cut-off date (21 November 2011), a total of 214 patients with haemophilia A had been exposed to turoctocog alfa in the clinical development programme. One (1) patient did not continue from the pharmacokinetic first human dose trial (Trial 3522) into the pivotal trial (Trial 3543) and does not contribute with clinical efficacy data. As of the cut-off date (21 November 2011), 11 patients had received turoctocog alfa during surgery (10 major surgeries and 1 minor surgery). Distribution of the flow of patients is shown in Figure 6.

Figure 6: Distribution of flow of patients in the clinical programme of turoctocog alfa



a) One patient was withdrawn from Trial 3600, and was allowed to continue in Trial 3568
b) 189 patients entered Trial 3568, but at the cut-off date (21 November 2011), one patient had dropped out prior to dosing and another patient did not yet have any information on treatment. Therefore FAS=187
c) One patient did not continue from Trial 3522 to Trial 3543. 12 patients did not continue from Trial 3543 to Trial 3568. 5 patients did not continue from Trial 3545 to Trial 3568

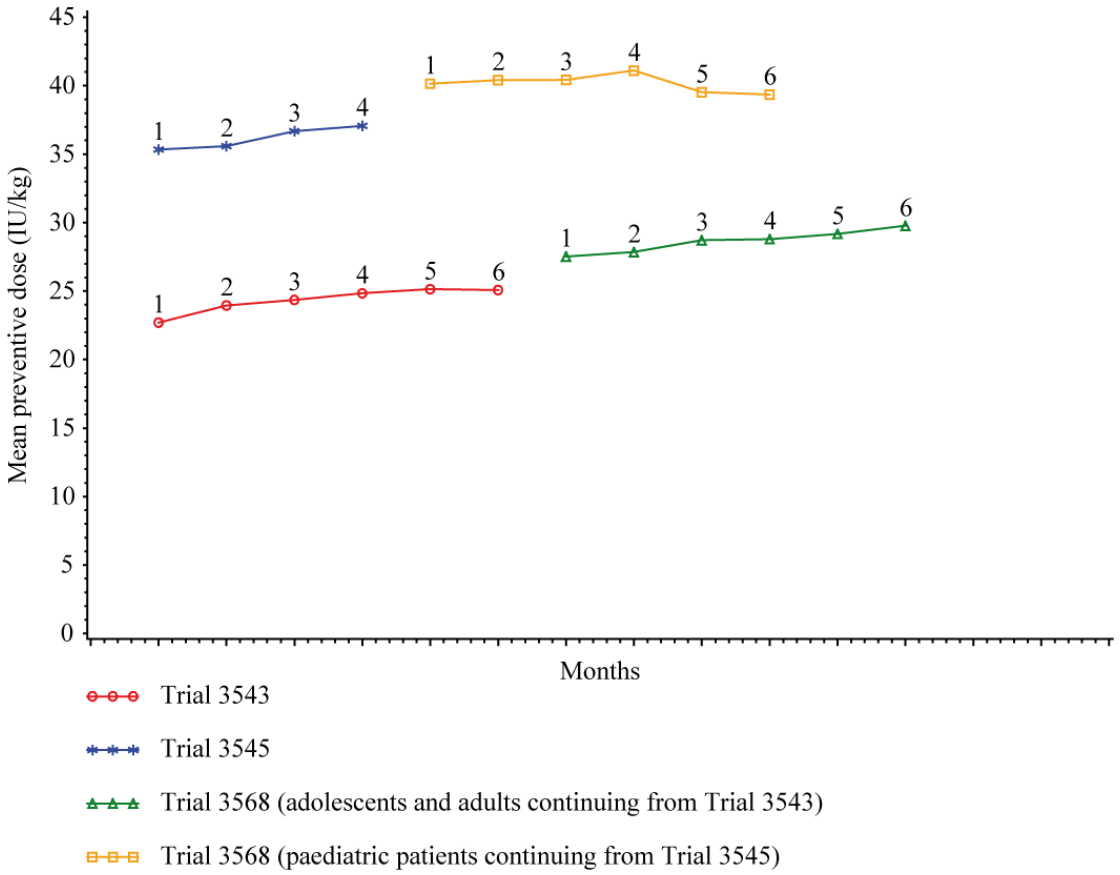
The trial populations were selected to represent previously treated patients with severe haemophilia A (FVIII activity ≤ 1%) without inhibitors. The trials were global and included patients from Brazil, Croatia, Germany, Israel, Italy, Japan, Lithuania, Macedonia, Malaysia, Poland, the Russian Federation, Republic of Serbia, Spain, Switzerland, Taiwan, Turkey, the UK and the US. The majority of the patients (82%) were White and of non-Hispanic/non-Latino ethnicity (80%).

A total of 66% of the patients had been on a prophylactic regimen, and 55% had been on an on-demand regimen prior to entering the turoctocog alfa programme (some patients had been on both regimens, explaining that the numbers do not sum up to 100%). Half of the patients on prophylaxis used recombinant FVIII products, while one-fourth of the patients on an on-demand treatment regimen used recombinant FVIII products.

Except for one adult patient, all patients with available data were hepatitis B negative. Among patients with available data on hepatitis C and HIV, all patients below 18 years of age were hepatitis C and HIV negative, whereas 58% of the adult patients were hepatitis C positive and 10% were HIV positive.

Consumption for prevention of bleeds

Figure 7: Mean consumption used for prevention per month during preventive regimen NN7008-3543, NN7008-3545 and NN7008-3568 pooled – Full analysis set



Annualised bleeding rate

A total of 991 bleeds were reported in 158 of the 213 patients. Traumatic bleeds were more frequent in children whereas spontaneous bleeds were more frequent in adolescents and adults. The majority of the bleeds were joint bleeds (72%).

The estimated annualised bleeding rate, when pooling data from Trials 3543, 3545 and 3568, was 4.89 bleeds/patient/year. However, the rates varied between the pivotal trials (6.50 bleeds/patient/ year in Trial 3543 and 5.33 bleeds/patient/year in Trial 3545) and the extension trial (3.54 bleeds/patient/year in Trial 3568). No association between age and annualised bleeding rate was apparent.

The estimated annualised bleeding rate varied considerably by country, with the lowest rate in Poland (1.18 bleeds/patient/year) and the highest rate in the Russian Federation (11.88 bleeds/patient/ year). No association between previous treatment regimen (on-demand, prophylaxis or both) and estimated annualised bleeding rate was observed that could explain the variation between the countries.

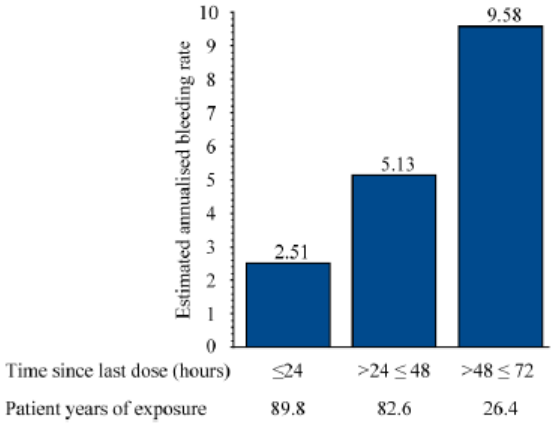
As of the cut-off date (21 November 2011), 68 patients had been on preventive treatment with turoctocog alfa for at least 12 months. The estimated annualised bleeding rate for these patients (4.29 bleeds/patient/year; 95% CI: 3.28−5.60 bleeds/patient/year) was comparable to the estimated annualised bleeding rate for the total trial population (4.89 bleeds/patient/year; 95% CI: 4.16−5.74

bleeds/patient/year), indicating that potential seasonal variation does not influence the overall estimate.

Bleeding rates by time since the latest preventive dose

Analyses of the estimated annualised bleeding rate within 24 hours, 24−48 hours and 48−72 hours after a prophylactic dose showed that the bleeding rate increased with time since the latest prophylactic dose. This further supports the finding of a strong prophylactic effect of turoctocog alfa treatment and indicates that a standard prophylactic regimen of treatment (every second day or three times weekly) is superior to a less frequent dosing regimen.

Figure 8: Analyses of the estimated annualised bleeding rate within 24 hours, 24−48 hours and 48−72 hours after a prophylactic dose



All 213 patients contributed with exposure in each group since all the patients had at least one period with 48 hours or more since their latest preventive dose.

Haemostatic effect

As a conservative approach, bleeds without reported outcomes were considered as treatment failures resulting in a success rate of 84.6% when pooling all trials. Excluding bleeds for which there were no reported outcomes (N=25) resulted in a success rate of 86.8%. A total of 898 (90.6%) of the bleeds were resolved with 1−2 infusions of turoctocog alfa, indicating that the clinical efficacy of turoctocog alfa in treatment of bleeds is similar to other rFVIII products.

Table 33: Haemostatic effect in treatment of bleeds – Trials NN7008-3543, NN7008-3545 and NN7008-3568 – Full analysis set

	Young children (0 - <6 years)	Older children (6 - <12 years)	Adolescents (12 - <18 years)	Adults (>= 18 years)	Total
Pooled trials					
Total number of bleeds (%)	65 (100.0)	96 (100.0)	99 (100.0)	731 (100.0)	991 (100.0)
Success rate (%)	61 (93.8)	82 (85.4)	78 (78.8)	617 (84.4)	838 (84.6)
Trial 3543					
Total number of bleeds (%)			67 (100.0)	432 (100.0)	499 (100.0)
Success rate (%)			48 (71.6)	355 (82.2)	403 (80.8)
Trial 3545					
Total number of bleeds (%)	53 (100.0)	73 (100.0)			126 (100.0)
Success rate (%)	51 (96.2)	65 (89.0)			116 (92.1)
Trial 3568					
Total number of bleeds (%)	12 (100.0)	23 (100.0)	32 (100.0)	299 (100.0)	366 (100.0)
Success rate (%)	10 (83.3)	17 (73.9)	30 (93.8)	262 (87.6)	319 (87.2)

In the calculation of the success rate, bleeds without reported haemostatic outcomes were considered as treatment failures.
Cross-reference: Appendix I, Table 24; Trial 3543 (M 5.3.5.2), Section 11.2.3.2; Trial 3545 (M 5.3.5.2), Section 11.2.3.2 and Trial 3568 (M 5.3.5.2), Section 11.2.2.2

Haemostatic effect by country

Following countries had a success rate below 80%: Brazil (79.5%), Israel (74.8%), Japan (66.7%), Taiwan (72.7%) and United Kingdom (77.8%). Apart from Israel (total patient n =159) the number of patients and number of bleeds in these countries were low.

Haemostatic effect by location of the bleed

The success rate was also investigated by the following locations: Joint, target joint, subcutaneous, muscular, gastrointestinal, mucosal and other. The success rates for the pooled trials (when bleeds without reported outcomes were considered as treatment failures) were 84.4% for joint bleeds, 85.0% for target joint bleeds (defined as 3 or more bleeds in the same joint within 6 months), 87.8% for subcutaneous bleeds, 85.7% for muscular bleeds, 86.2% for bleeds where the location of the bleed was reported as “other” and 80% for bleeds where the location of the bleed was not reported. Few gastrointestinal and mucosal bleeds (5 and 10 bleeds, respectively) were reported and the corresponding success rates were 60% and 90%.

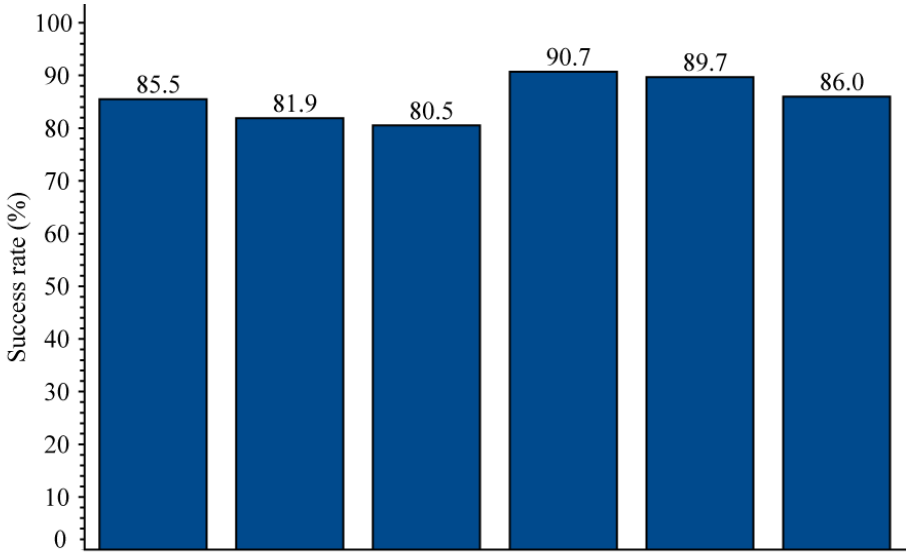
Haemostatic effect by cause of bleed

The success rate (rated as “excellent” or “good”) was similar for spontaneous bleeds (84.3%) and traumatic bleeds (85.8%) for the pooled trials.

Haemostatic effect by time on turoctocog alfa

A plot of the success rate by number of months that the patients had been on turoctocog alfa treatment showed that there was no consistent increase or decrease of the haemostatic effect over time (Figure 9).

Figure 9: Success rate by number of months that the patients had been on turoctocog alfa treatment

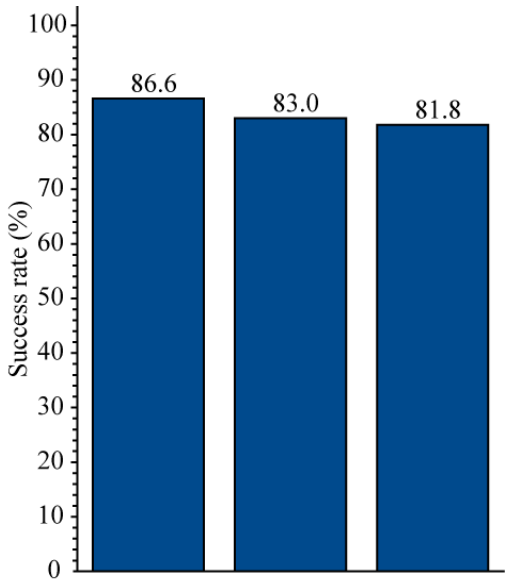


Months on turoctocog alfa treatment	<3	3-6	6-9	9-12	12-15	≥15
Number of bleeds in each period	359	254	128	75	39	136

Haemostatic effect by time from onset of a bleed to treatment of the bleed

The success rate was investigated by the time elapsed from the onset of the bleed and until the treatment with turoctocog alfa was initiated and a decrease in the success rate with increased time from onset of the bleed until treatment can be seen (Figure 10).

Figure 10: Success rate of treatment of bleeds by time from onset of bleed until treatment with turoctocog alfa – Trials NN7008-3543, NN7008-3545 and NN7008-3568 – Full analysis set



Hours from onset of bleed to treatment	<2	2 - 4	>4
Number of bleeds in each period	621	159	176

The remaining 35 bleeds did not have start time for the bleed or start time of the treatment

Efficacy in surgery

A total of 11 surgeries were performed in 11 patients, of which 10 were major surgeries and 1 was minor. Except for 1 adolescent patient, all patients undergoing surgery were adults. The surgery indications included arthropathy and chronic pain in the left knee for 1 patient, synovitis for 1 patient, semi-impacted tooth and removal of tooth root for 1 patient, arthropathy for 4 patients, circumcision for 1 patient, recurrent haemarthrosis for 1 patient, pain in left ankle for 1 patient and poly-trauma for 1 patient. Haemostasis was successful (haemostatic effect was rated as excellent or good) in all the surgeries, indicating that turoctocog alfa has a significant haemostatic effect both during and after surgery.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The three main trials were designed as open label, single arm studies evaluating the efficacy and safety of turoctocog alfa. Originally, the primary objective of the studies was efficacy and evaluating prevention of bleeds as well as treatment of bleeds. This changed to safety with Amendment 14 (dated 15-Oct-2009) and all efficacy parameters were proposed as secondary endpoints, whereas

immunogenicity was chosen as primary endpoint. According to the scientific advice letters (EMA/CHMP/SAWP/14717/2010, EMA/CHMP/SAWP/287098/2010, EMA/423638/2010), the CHMP did not agree with this proposal. Therefore, clinical efficacy data submitted was considered as the primary endpoint when assessing the results of the trial. In general, the studies were conducted in accordance with the guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (EMEA/CHMP/BPWP/144533/2009).

Efficacy data and additional analyses

When pooling data from all submitted trials investigating efficacy of turoctocog alfa (NN7008-3543, NN7008-3545 and NN7008-3568) the estimated annualised bleeding rate was 4.89 bleeds/patient/year. Due to the large variation in the annualised bleeding rate between patient, the median rates were also taken into account as relevant. The total median bleeding rate was 3.66 bleeds/patient/year which was considerably lower than the mean bleeding rate. The success rate (defined as haemostatic effect rated as good or excellent) was 84.6% across all trials and most of the bleeds (90.6%) were resolved with 1-2 infusions. Efficacy data for on-demand treatment were not available.

The preventive dose regimens chosen for adolescents and adults in Trial NN7008-3543 were 20-40 IU/kg every second day or 20-50 IU/kg three times per week. The preventive dose regimens chosen for paediatric patients in Trial NN7008-3545 were 25-50 IU/kg every second day or 25-60 IU/kg three times per week. In the extension trial the dose regimen for prevention also differed slightly: 20−50 IU/kg every second day or 20−60 IU/kg 3 times weekly. These differences are reflected by the consumption data. The mean dose used for prevention showed that the administered dosage in the paediatric trial NN7008-3545 (36.8 IU/kg) was significantly higher than in the pivotal trial NN7008-3543 (24.4 IU/kg). Further, the mean preventive dose was also increased in the extension study NN7008-3548 (30.4 IU/kg). A similar relation is observed for the mean consumption per patient per year during prevention and the mean consumption from start to stop of a bleed. In general, the estimated annualised bleeding rates of the main trials were regarded to be in an acceptable range. The observed annualised bleeding rates from the pivotal study in adults and the paediatric study were higher than in the extension study. An increase of the preventive dose for the adult and the paediatric participants entering the extension trial might be the reason for the different annualised bleeding rates. The mean difference appears low. The majority of patients in the turoctocog alfa clinical trials were on the three times weekly regimen, which reflects the clinical practice. When pooling all trial data, no difference was observed in the annualised bleeding rate for patients on every second day regimen compared to the three times weekly regimen (includes one period >48 hours). Both regimens were considered appropriate.

The general details of the bleeds are regarded comparable for the full analysis set and the individual studies. Overall, the success rates of the treatment of bleeds using turoctocog alfa are in an acceptable range. In the pivotal trial NN7008-3543 the haemostatic response was rated as none in 12 bleeding episodes in 6 patients. One patient, who experienced five bleedings with no response was not very compliant. The bleedings with a haemostatic response rated as 'none' were all treated with only 1-2 infusions with the exception of one. This last case could partially be explained by the misinterpretation of musculoskeletal pain as a bleed. The haemostatic response and success rate was also investigated by a number of other factors. The success rate for mucosal bleeds and bleeds with the location reported as "other" was lower. Apart from Israel, there were no noteworthy differences in success rates among countries. The haemostatic response by time from onset of bleed to the first trial drug administration for

treatment of the bleed did not show apparent differences between patients. The calculated mean time to control a bleed is in an acceptable range. 90.6% of the bleeds were resolved with 1-2 infusions of turoctocog alfa, which is regarded as a good and sufficient response. The number of infusions required to stop a bleeding does not fully correspond to the rating of the haemostatic response e.g. rating excellent and the requirement of 2 or more infusions. However, these small inconsistencies are usually observed in such kind of studies. The mean haemoglobin levels 1 hour and 24 hours after surgery were 9.4% and 16.2% lower, respectively. These values might however be influenced by changes in the total fluid balance of the body.

2.5.4. Conclusions on the clinical efficacy

Efficacy of turoctocog alfa is supported by the data on consumption, annualized bleeding rates and haemostatic response and success rates. The results presented for the individual trials as well as for the pooled data are considered robust and support the assumption of effective prophylaxis as well as treatment of breakthrough bleeds and protection during surgery. Efficacy data for on-demand treatment were not available. The CHMP recommends to include at least 10 PTPs receiving on-demand treatment in the extension trial and evaluate the bleeding pattern and the consumption data for a minimum of 6 months. The results can be provided post-marketing.

The safety and efficacy of NovoEight in previously untreated patients have not yet been established. No data are available. This is reflected in the RMP as missing information.

Based on the clinical trial data, the proposed dosing range for turoctocog alfa is supported and thus no dose adjustment is required. Treatment should be initiated under the supervision of a doctor experienced in the treatment of haemophilia. No difference was observed in the annualised bleeding rate for patients on every second day regimen compared to the three times weekly regimen (includes one period >48 hours). Therefore, both dosing regimens are considered appropriate.

2.6. Clinical safety

Patient exposure

Overall 214 patients had a total of 32,929 exposure days during prevention and for treatment of bleeds to turoctocog alfa in all the applicant-sponsored clinical trials up to 21 November 2011 as the cut-off date for ongoing trials.

Table 33: Number of patients exposed in each of the clinical trials with turoctocog alfa – Safety analysis set

Trial	Single dose*		Preventive regimen (multiple dose)**	Surgery***
	turoctocog alfa	Advate ®	turoctocog alfa	turoctocog alfa
NN7008-3522	23	23		
NN7008-3893[2]	4			
NN7008-3600[2]	7			
NN7008-3543			150	9
NN7008-3545			63	
NN7008-3568[1]			187	2

[1]Ongoing extension trial to Trials NN7008-3543 and NN7008-3545. Number of patients exposed as of the cut-off date (21 November 2011).
[2]The pharmacokinetic measurements were based on a single dose of turoctocog alfa. However, patients participating in these two trials received preventive treatment with turoctocog alfa during the period between the screening visit and the pharmacokinetic session. In addition to the preventive doses, three bleeds were treated with turoctocog alfa in Trial 3600 and two bleeds were treated with turoctocog alfa in Trial 3893.

Adverse events

A total of 503 adverse events were reported in 154 patients during prevention and treatment of bleeds. The overall rate was 2.45 adverse events per patient year of exposure.

Table 34: Overview of adverse events reported during prevention and treatment of bleeds: Trials 3522, 3893, 3600, 3543, 3545 and 3568 pooled – Safety analysis set

	0 - <6 Years N (%) E [R]		6 - <12 Years N (%) E [R]		12 - <18 Years N (%) E [R]		>=18 Years N (%) E [R]		Total N (%) E [R]	
Number of patients	31		32		24		127		214	
Total patient years of exposure	15.3		18.9		24.4		146.4		205.0	
All adverse events	19 (61.3)	54 [3.53]	18 (56.3)	46 [2.44]	19 (79.2)	66 [2.71]	98 (77.2)	337 [2.30]	154 (72.0)	503 [2.45]
Serious adverse events	3 (9.7)	3 [0.20]	2 (6.3)	2 [0.11]	3 (12.5)	3 [0.12]	9 (7.1)	13 [0.09]	17 (7.9)	21 [0.10]
Adverse events by severity										
Severe	1 (3.2)	1 [0.07]	1 (3.1)	1 [0.05]	0 (0.0)	0 [0.00]	9 (7.1)	11 [0.08]	11 (5.1)	13 [0.06]
Moderate	6 (19.4)	7 [0.46]	4 (12.5)	5 [0.27]	7 (29.2)	15 [0.62]	47 (37.0)	73 [0.50]	64 (29.9)	100 [0.49]
Mild	16 (51.6)	45 [2.94]	17 (53.1)	40 [2.12]	18 (75.0)	51 [2.09]	85 (66.9)	253 [1.73]	136 (63.6)	389 [1.90]
Missing	1 (3.2)	1 [0.07]	0 (0.0)	0 [0.00]	0 (0.0)	0 [0.00]	0 (0.0)	0 [0.00]	1 (0.5)	1 [0.00]
Adverse events by relation										
probably or possibly related	1 (3.2)	2 [0.13]	0 (0.0)	0 [0.00]	0 (0.0)	0 [0.00]	16 (12.6)	24 [0.16]	17 (7.9)	26 [0.13]
Unlikely related	19 (61.3)	52 [3.40]	18 (56.3)	46 [2.44]	19 (79.2)	66 [2.71]	95 (74.8)	313 [2.14]	151 (70.6)	477 [2.33]
Adverse events										
Leading to withdrawal	0 (0.0)	0 [0.00]	0 (0.0)	0 [0.00]	0 (0.0)	0 [0.00]	2 (1.6)	2 [0.01]	2 (0.9)	2 [0.01]

N: Number of patients with adverse events
%: Proportion of patients with adverse event
E: Number of adverse events
R: Number of adverse events per patient years of exposure
Adverse events during surgery are not included

The most commonly reported adverse events were related to dosing (incorrect dose administered [0.13 events per patient year of exposure], wrong technique in drug usage process [0.01 event per patient year of exposure], overdose [0.01 event per patient year of exposure], underdose [0.01 event per patient year of exposure] and injection site extravasation [1 event]), headache (0.17 events per patient year of exposure) and nasopharyngitis (0.15 events per patient year of exposure). The overall rate of adverse events decreased over months on turoctocog alfa treatment. No differences in the safety profile of turoctocog alfa have been observed between children and adults. The overall rate of adverse events was, however, slightly higher for the young children (0≤6 years) (3.53 events per patient year of exposure) as compared to the other age groups. Events reported more frequently in young children as compared to the other age groups included upper respiratory tract infection, pyrexia, vomiting, cough and ear pain. Two events in one child (contusion and incorrect dose administered) were evaluated as possibly or probably related to trial product by the investigator.

A total of 26 adverse events in 17 patients were evaluated by the investigator as possibly or probably related to trial product. These events occurred in Trials NN7008-3522, NN7008-3543, NN7008-3545 and NN7008-3568. The most frequently reported events evaluated by the investigator as possibly or probably related to trial product were injection site erythema, pyrexia and increased hepatic enzymes. During the review, it was observed that 18 adverse events of increased hepatic parameters (defined as alanine aminotransferase, aspartate aminotransferase, bilirubin conjugated, blood alkaline

phosphatase, total bilirubin, hyperbilirubinaemia, gamma-glutamyltransferase and “hepatic enzymes increased”) were recorded for 10 patients. The majority (8/10=80%) of these patients were positive for hepatitis C. Most of these events (14/18=78%) were evaluated by the investigator as unlikely related to trial product. Four (4) events of increased levels of hepatic enzymes in 3 patients were recorded by the investigator as probably or possibly related to trial product.

Table 35: Summary of adverse events possibly o probably related to trial product: Trials 3522, 3893, 3600, 3543, 3545 and 3568 pooled – Safety analysis set

	0 - <6 Years N (%) E [R]	6 - <12 Years N (%) E [R]	12 - <18 Years N (%) E [R]	>=18 Years N (%) E [R]	Total N (%) E [R]
Number of patients	31	32	24	127	214
Total patient years of exposure	15.3	18.9	24.4	146.4	205.0
All adverse events	1(3.2) 2[0.13]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	16(12.6) 24[0.16]	17(7.9) 26[0.13]
General disorders and administration site conditions	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	6(4.7) 8[0.05]	6(2.8) 8[0.04]
Fatigue	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	1(0.8) 1[0.01]	1(0.5) 1[0.00]
Feeling hot	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	1(0.8) 1[0.01]	1(0.5) 1[0.00]
Injection site erythema	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	3(2.4) 3[0.02]	3(1.4) 3[0.01]
Oedema peripheral	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	1(0.8) 1[0.01]	1(0.5) 1[0.00]
Pyrexia	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	2(1.6) 2[0.01]	2(0.9) 2[0.01]
Injury, poisoning and procedural complications	1(3.2) 2[0.13]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	3(2.4) 3[0.02]	4(1.9) 5[0.02]
Contusion	1(3.2) 1[0.07]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	1(0.5) 1[0.00]
Incorrect dose administered	1(3.2) 1[0.07]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	3(2.4) 3[0.02]	4(1.9) 4[0.02]
Investigations	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	4(3.1) 5[0.03]	4(1.9) 5[0.02]
Alanine aminotransferase increased	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	1(0.8) 1[0.01]	1(0.5) 1[0.00]
Aspartate aminotransferase increased	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	1(0.8) 1[0.01]	1(0.5) 1[0.00]
Heart rate increased	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	1(0.8) 1[0.01]	1(0.5) 1[0.00]
Hepatic enzyme increased	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	2(1.6) 2[0.01]	2(0.9) 2[0.01]
Nervous system disorders	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	2(1.6) 2[0.01]	2(0.9) 2[0.01]
Dizziness	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	1(0.8) 1[0.01]	1(0.5) 1[0.00]
Headache	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	1(0.8) 1[0.01]	1(0.5) 1[0.00]
Vascular disorders	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	2(1.6) 2[0.01]	2(0.9) 2[0.01]
Hypertension	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	1(0.8) 1[0.01]	1(0.5) 1[0.00]
Lymphoedema	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	1(0.8) 1[0.01]	1(0.5) 1[0.00]
Cardiac disorders	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	1(0.8) 1[0.01]	1(0.5) 1[0.00]
Sinus tachycardia	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	1(0.8) 1[0.01]	1(0.5) 1[0.00]
Musculoskeletal and connective tissue disorders	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	1(0.8) 1[0.01]	1(0.5) 1[0.00]
Musculoskeletal stiffness	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	1(0.8) 1[0.01]	1(0.5) 1[0.00]
Psychiatric disorders	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	1(0.8) 1[0.01]	1(0.5) 1[0.00]
Insomnia	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	1(0.8) 1[0.01]	1(0.5) 1[0.00]
Skin and subcutaneous tissue disorders	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	1(0.8) 1[0.01]	1(0.5) 1[0.00]
Rash	0(0.0) 0[0.00]	0(0.0) 0[0.00]	0(0.0) 0[0.00]	1(0.8) 1[0.01]	1(0.5) 1[0.00]

N: Number of patients with adverse events
%: Proportion of patients with adverse events
E: Number of adverse events
R: Number of adverse events per patient years of exposure
Adverse events during surgery is not included

A total of 13 events in 11 patients were rated as severe (melaena, upper gastrointestinal haemorrhage, road traffic accident, suicide attempt, depression, arthropathy, blood glucose increased, glucose urine present, sinusitis, femur fracture, peripheral artery aneurysm, fall, muscle haemorrhage, intestinal haemorrhage and tympanic membrane perforation). These events were all evaluated as unlikely related to trial product by the investigator.

Adverse events during surgery

As the cut-off date (21 November 2011), a total of 11 patients (1 adolescent and 10 adult patients) were included in the surgery sub-trials (Trials NN7008-3543, NN7008-3568). These patients had a total of 210 exposure days to turoctocog alfa (mean: 18.3 exposure days per patient).

A total of 5 adverse events were recorded in 5 patients during surgery. All events were evaluated by the investigator as unlikely related to trial product.

Table 36: Listing of adverse events during surgery: trials NN7008-3543 and NN7008-3568 – safety analysis set

Patient	Age	Preferred Term	Relationship	Severity	Outcome
Trial 3543					
A	36	Paraesthesia	Unlikely	Mild	Recovered
B	25	Haemorrhage	Unlikely	Moderate	Recovered
C	18	Allergy to chemicals	Unlikely	Mild	Not Recovered
Trial 3568					
A	24	Arthralgia	Unlikely	Mild	Recovered
B	55	Vomiting	Unlikely	Mild	Recovered
Age refers to the age of the patient at first visit in first trial.					

Serious adverse event / deaths / other significant events

Deaths

As of the 1 May 2012 one death had occurred during the trials. This event concerned a 27-year-old patient in Trial NN7008-3568. This patient was brought to the hospital in a state of unconsciousness (Glasgow coma scale 7) and was bleeding from the right scalp/temporal area. The cause of the trauma was alleged to be an assault and a cranial computerised tomography (CT) scan revealed a right-sided fronto-temporal parietal subdural haemorrhage with midline shift, mixed density and cerebral edema. The patient underwent an emergency (right) decompressive craniotomy with evacuation of the haematoma. The patient was covered with trial medication preoperatively and continued post-operatively till he was declared dead 2 days after arrival at the hospital.

No other fatal events occurred during the trials.

Other serious adverse events

A total of 21 serious adverse events were recorded in 17 patients in Trials NN7008-3543, NN7008-3545 and NN7008-3568 corresponding to a rate of 0.10 serious adverse events per patient year of exposure. The serious adverse events occurred after 11 to 368 turoctocog alfa exposure days and no association between frequency of the events and exposure time was observed (Table 37). No serious adverse events were recorded in the pharmacokinetic Phase 1 trials.

Table 37: Listing of serious adverse events reported during prevention and treatment of bleeds: Trials 3522, 3893, 3600, 3543, 3545 and 3568 – Safety analysis set

Patient number	Age	Preferred term	ED[1]	Relation-ship	Severity	Outcome
Trial 3543						
101004	20	Melaena	60	Unlikely	Severe	Recovered
101005	24	Upper gastrointestinal haemorrhage	86	Unlikely	Severe	Recovered
121101	26	Hypertension	28	Possible	Moderate	Recovered
		Sinus tachycardia	28	Possible	Moderate	Recovered
		Insomnia	28	Possible	Moderate	Recovered
184101	58	Melaena	11	Unlikely	Mild	Recovered
201003	21	Road traffic accident	17	Unlikely	Severe	Recovered
251102	23	Suicide attempt**	90	Unlikely	Severe	Recovered
656104	13	Fall	66	Unlikely	Moderate	Recovered
861102	36	Hepatic enzyme increased	84	Probable	Moderate	Recovering
Trial 3545						
121504	4	Soft tissue injury	46	Unlikely	Moderate	Recovered
355500	3	Gastroenteritis viral	35	Unlikely	Moderate	Recovered
866501	7	Device related infection	57	Unlikely	Mild	Recovered
Trial 3568						
181001	22	Injury	324	Unlikely	Moderate	Not yet recovered[2]
		Psychotic disorder	368	Unlikely	Moderate	Not recovered[3]
202001	28	Scrotal pain	237	Unlikely	Mild	Recovered
202003	55	Fall*	190	Unlikely	Severe	Not recovered[2]
		Femur fracture	190	Unlikely	Severe	Not recovered[2]
		Hand fracture	190	Unlikely	Moderate	Not recovered[2]
281500	7	Muscle haemorrhage	124	Unlikely	Severe	Recovered
281501	3	Intestinal haemorrhage	133	Unlikely	Severe	Recovered
701103	17	Skin injury	99	Unlikely	Moderate	Recovered
703101	15	Road traffic accident	244	Unlikely	Moderate	Not yet recovered[2]

The relationship was judged by the investigator. Age refers to the age of the patient at first visit in first trial.[1]ED: Number of exposure days before onset of event. [2]The outcome of these events was recorded as 'not yet recovered' or 'not recovered' at the cut-off date for this trial (21 November 2011). Follow-up inquiries confirmed that the patients recovered from these events.[3]Patient had a chronic psychotic disorder.

Please note that 23 events are listed in this table, whereas 21 serious adverse events are reported in all summary tables. The two additional events included here are 'fall' (Patient number 202003, Trial 3568),* which was marked as linked to the two events of femur fracture and hand fracture and 'suicide attempt' (Patient number 251102, Trial 3543),** which was linked to a non-serious adverse event of depression. Furthermore, please note that for Trial 3545, the presented numbers for EDs before onset of event differ from those presented in the clinical trial report, where EDs were calculated as calendar days.

A total of 4 serious adverse events in 4 patients were reported in Trial NN7008-3568 between the individual cut-off dates (last visit before 21 November 2011) and 1 May 2012. The serious adverse events were subdural haemorrhage, cellulitis/staphylococcal infection, pancreatitis and cholelithiasis. The outcome of one of the serious adverse events (subdural haemorrhage) was fatal (see deaths). All four events were regarded as unlikely related to turoctocog alfa administration.

No thromboembolic events or allergic type hypersensitivity reactions against turoctocog alfa occurred during all trials.

Laboratory findings

Overall, no clinically relevant changes associated with exposure to trial product have been observed for parameters of haematology, biochemistry and urinalysis in any of the clinical trials with turoctocog alfa.

Haematology

Haematology was assessed in all trials. In NN7008-3522, one patient experienced 3 adverse events of decrease in red blood cell count, haemoglobin and haematocrit. These events were observed 49 hours after administration of turoctocog alfa. All events were reported as unlikely related to trial product by the investigator and the patient recovered from all events. Furthermore, several patients had low haemoglobin levels at baseline and/or during the trial.

An adverse event of increased neutrophil count was reported for one patient in NN7008-3545. In addition, an adverse event of increased white blood cell count was recorded for one patient in NN7008-3568. Both patients recovered from these events.

Biochemistry

Biochemistry was assessed in all trials. A total of 18 adverse events of increased hepatic parameters were reported during NN7008-3543 and NN7008-3568 in 10 patients, reflecting a relatively high proportion of patients (58% of the adult patients) with positive hepatitis C antibody tests. In NN7008-3893, one patient experienced increased levels of blood glucose. This was reported as an adverse event.

Urinalysis

Urinalysis was performed in trials NN7008-3522, NN7008-3600 and NN7008-3543. A few abnormal findings were observed in trial 3600 (blood and bilirubin in urine of one patient). None of these findings were considered clinically significant by the investigator. No clinically relevant changes over the trial period were apparent in trials NN7008-3522 and NN7008-3543.

Safety in special populations

Intrinsic factors

No differences in the safety profile of turoctocog alfa have been observed between children and adults. No inhibitors were observed in any of the patients. As all patients were males with severe haemophilia A, no analyses of safety by sex or severity of disease could be performed.

Use in pregnancy and lactation

Based on the rare occurrence of haemophilia A in women, experience regarding the use of turoctocog alfa during pregnancy has not been evaluated in clinical trials.

Immunological events

FVIII inhibitors

The immunogenicity of turoctocog alfa was assessed throughout the development programme, and tests for FVIII inhibitors were performed in all clinical trials. All cases of inhibitors were to be recorded as adverse events. As of the 1 May 2012, no patients developed FVIII inhibitors. Furthermore, no signs of early inhibitor development were observed as evaluated by FVIII activity (incremental recovery), and the pharmacokinetic results of 15 patients in trial NN7008-3543 (3–6 month after first injection of

turoctocog alfa) were comparable to the results obtained after the first dose of turoctocog alfa in trial NN7008-3522.

In trial NN7008-3545, one patient had a positive FVIII inhibitor test at visit 4, however, the results of a second separately drawn sample was negative, meaning that the definition of FVIII inhibitors was not met. The positive FVIII inhibitor test at visit 4 was reported as an adverse event and as a medical event of special interest. The patient was withdrawn from the trial due to treatment with a FVIII concentrate other than turoctocog alfa (trial withdrawal criteria). A further blood sample was tested and found to be negative, when the patient had his final visit (visit 8) following the decision to withdraw him from the trial.

Other antibodies

Assessments for development of anti-host cell protein antibodies (anti-CHO antibodies and anti-murine IgG antibodies) were performed at regular time points during trials NN7008-3522, NN7008-3543 and NN7008-3545. A total of 19 patients were at some point during the trials positive for anti-CHO antibodies. Of these, 2 patients changed from anti-CHO negative to anti-CHO positive and 6 patients changed from anti-CHO positive to anti-CHO negative. The remaining 11 patients were either positive throughout the trials (N=6), negative at baseline and end-of trial but with transient positive samples (N=2) or positive at baseline and end-of trial but with negative samples in between (N=3). No patients changed from anti-murine IgG negative to positive during the trials.

Safety related to drug-drug interactions and other interactions
No interaction studies were submitted.

Discontinuation due to adverse events
Two patients (0.9%) were withdrawn due to adverse events.

One patient was withdrawn due to an adverse event of fatigue lasting for about 24 hours after every infusion of turoctocog alfa. The event was evaluated as mild and possibly related to trial product.

The other patient was withdrawn after 368 exposure days due to a chronic psychotic disorder which was evaluated as moderate and unlikely related to the trial product.

Post marketing experience
N/A

2.6.1. Discussion on clinical safety

The design of the clinical trials that contribute to the safety database is according to guideline requirements. Non-controlled studies are acceptable in the small haemophilia A population in order to gain sufficient exposure with the new coagulation factor and to not spend some of the rare patients on an already established FVIII product. Adult and paediatric patients have been sufficiently exposed to turoctocog alfa.

During all clinical studies a total of 30 adverse reactions were reported in 19 of 214 patients exposed into turoctocog alfa. The most frequently reported adverse reactions were injection site reactions and

hepatic enzymes increased. Of the 30 adverse reactions, 2 were reported in 1 out of 31 patients below 6 years of age, none in patients from 6 to 18 years of age and 28 were reported in 16 out of 127 adults.

The observed adverse event profile is considered similar to that of other licensed FVIII products and did not give rise to concern. The following adverse events were designated as medical events of special interest (MESIs) in all trials: medication errors; suspected transmission of an infectious agent via a trial product; thromboembolic events; formation of FVIII inhibitors; allergic type hypersensitivity reactions, including anaphylaxis/anaphylactoid reactions.

The summary of safety profile includes: hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed rarely and may in some cases progress to severe anaphylaxis (including shock).

In clinical studies involving 63 paediatric patients between 0 and 12 years of age and 24 adolescents between 12 and 18 years of age with severe haemophilia A no difference in the safety profile of turoctocog alfa was observed between paediatric patients and adults.

In all trials 34 medication errors were reported, most of them were dosing errors. The applicant stated that no adverse events have been associated with medication errors. They were related to trial procedures or errors of human error nature. In contrast to the clinical trial programme turoctocog alfa will be marketed as powder in a vial for reconstitution together with 4.3 ml solvent in a prefilled syringe with a scale, which will minimize dosing errors. Together with the instruction for use the applicant believes that the preventative measures are appropriate to mitigate and minimise the risk of medication errors. This explanation is acknowledged and for the time being no further statement in the SmPC is regarded necessary.

The observed increase of hepatic parameters of several patients can mainly be explained by positive hepatitis C antibody tests. The frequency of headache-episodes within all study-phases was relatively high. But, only one event of headache was reported by the investigator to be probably related to turoctocog alfa. In addition, there was no association to the most recent dose of turoctocog alfa. Infusion speed was not recorded.

The presented analysis of serious adverse events includes one fatal case which is acceptable and is consistent with the anticipated safety-profile.

Allergic type hypersensitivity reactions are possible with turoctocog alfa. The product contains traces of hamster proteins, which in some patients may cause allergic reactions. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

In case of shock, standard medical treatment for shock should be implemented.

No clinically relevant dose-related changes have been observed for parameters of haematology, biochemistry and urinanalysis.

There was one patient with a positive initial FVIII inhibitor test. But, this sole result could not be repeated by a test of a new blood sample. In addition, no influence on FVIII activity could be observed at the time of the positive inhibitor test. Therefore, a laboratory error or other interferences might be

a possible explanation. In conclusion, no inhibitor development was detected in any patient treated with turoctocog alfa.

The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the exposure to factor VIII, the risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observation and laboratory test. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors.

It is strongly recommended that every time that turoctocog alfa is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the medicinal product.

Development of anti-host cell protein antibodies was observed in some patients at different time points. Only few patients changed from anti-CHO negative to anti-CHO positive or had transient positive anti-CHO results.

Turoctocog alfa should not be used if the patient is hypersensitive to the active substance or to any of the excipients listed in section 6.1 of the SmPC or for known allergic reaction to hamster protein.

After reconstitution this medicinal product contains 0.31 mmol sodium (7 mg) per ml of reconstituted solution. To be taken into consideration by patients on a controlled sodium diet.

No interaction studies have been performed with turoctocog alfa.

No symptoms of overdose with recombinant coagulation factor VIII have been reported.
From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via their national reporting systems.

2.6.2. Conclusions on the clinical safety

Clinical safety has been analysed from the data of all clinical trials. Evaluation in general follows the currently valid clinical guideline. The presented results are considered to be acceptable. No

unexpected patterns in the reported adverse events and serious adverse events were observed. The safety and tolerability of turoctocog alfa treatment displays no differences between children and adults. As of the cut-off date (1 May 2012), no patients developed FVIII inhibitors or thromboembolic events. The safety database is considered to be sufficient to support the marketing authorisation of turoctocog alfa.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 3.0, the PRAC considers by consensus that the risk management system for turoctocog alfa (NOVOEIGHT) in the treatment and prophylaxis of bleeding in patients with haemophilia A is acceptable.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

Summary of safety concerns	
Important identified risks	Inhibitor development
	Allergic/hypersensitivity reactions
Important potential risks	Mix-up of different strengths
Missing information	Elderly patients
	Previously untreated patients
	Patients with HIV (CD4 < 200 cells/µL) or HCV (viral load > 200 particles/µL)
	Patients with renal or hepatic insufficiency
	Patients with mild and moderate haemophilia
	Use in females with haemophilia A, including pregnant and breast-feeding women
	ITI therapy

Abbreviations: CD4 = cluster of differentiation 4; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ITI = immune tolerance therapy.

- **Pharmacovigilance plans**

Table 3–6 Ongoing and planned additional pharmacovigilance studies/activities in the pharmacovigilance plan

Study/activity type Title Category (1-3)	Objectives	Safety concerns addressed	Status, Date for submission of interim or final reports
Clinical trial **NN7008-3809** Safety and efficacy of turoctocog alfa in prevention and treatment of bleeds in paediatric previously untreated patients with haemophilia A. Category 3	- Incidence rate of FVIII inhibitors - Frequency of adverse events - Haemostatic effect on treatment of bleeds - Annualised bleeding rate	- Inhibitor development - Allergic/hypersensitivity reactions - PUPs - ITI therapy	Planned Final report (planned): 10 Feb 2017
PASS **NN7008-3553** A multi-centre non-interventional study of safety and efficacy of turoctocog alfa during long-term treatment of severe and moderately severe haemophilia A (FVIII < 2%). Category 3	- Incidence rate of FVIII inhibitors - Frequency of adverse events - Haemostatic effect on treatment of bleeds - Annualised bleeding rate	- Inhibitor development - Allergic/hypersensitivity reactions - Mix-up of different strengths - Elderly patients - Patients with renal or hepatic insufficiency - Patients with moderate haemophilia	Planned Final report (planned): 02 Aug 2018

Abbreviations: FVIII = factor VIII; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ITI = immune tolerance induction; PASS = post-authorisation safety study; PUPs = previously untreated patients.

- **Risk minimisation measures**

Table 5–11 Summary of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Identified risks		
Inhibitor development	SmPC Section 4.4: • "The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per mL of plasma using the modified assay. The risk of developing inhibitors is correlated to the exposure to factor VIII, the risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days." • "Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch." • "In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observation and laboratory test. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors."	None
Allergic/ hypersensitivity reactions	SmPC Section 4.3: • "Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Known allergic reaction to hamster protein." SmPC Section 4.4: "Allergic type hypersensitivity reactions are possible with NovoEight®. The product contains traces of hamster proteins, which in some patients may cause allergic reactions. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. In case of shock, standard medical treatment for shock should be implemented."	
Potential risks		
Mix-up of different strengths	Package leaflet: • "Check the name, strength and colour of the package, to make sure it contains the correct product."	None
Missing information		
Elderly patients	SmPC Section 4.2: • "There is no experience in patients > 65 years."	None
PUPs	SmPC Section 4.2: • "The safety and efficacy of NovoEight® in previously untreated patients have not yet been established. No data are available."	None
Patients with severe HIV or HCV	None	None
Patients with renal or hepatic insufficiency	None	None
Patients with mild and moderate haemophilia A	None	None
Use in females	SmPC Section 4.6: • "Animal reproduction studies have not been conducted with NovoEight®. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breastfeeding is not available. Therefore, factor VIII should be used during pregnancy and breast-feeding only if clearly indicated."	None
Use in ITI therapy	None	None

Abbreviations: SmPC = summary of product characteristics; CD4 = cluster of differentiation 4; FVIII = factor VIII; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ITI = immune tolerance induction; PUPs = previously untreated patients.

The CHMP endorsed this advice without changes.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Turoctocog alfa, a newly developed recombinant Factor VIII with a 21 amino acid residue truncated B-domain, is intended for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Pharmacokinetic properties of turoctocog alfa were found to be similar to that of other licensed FVIII products. Furthermore, in the main three clinical trials, turoctocog alfa was shown to prevent and treat bleedings in paediatric and adults with severe Haemophilia A as well as maintaining haemostasis in haemophilia A patients during surgery. The safety database submitted in the application provides sufficient information on the adverse events associated with turoctocog alfa treatment. No significant risks have been identified regarding the safety and tolerability of turoctocog alfa as compared to similar Factor VIII products.

Uncertainty in the knowledge about the beneficial effects

Patients receiving on-demand treatment were not included in the studies. In contrast to prophylaxis patients, who experience late bleeds, on-demand patients may stay on very low endogenous factor VIII levels for a long time and will differ in their needs and consumption in the case of a bleed. Since more than 50% of adult haemophilia A patients require on-demand treatment, the administration of turoctocog alfa for on-demand treatment should be addressed. Further, the overall frequency and pattern of bleeds during on-demand treatment should also be investigated as it will differ compared to breakthrough bleeding during prophylactic treatment. Therefore, the CHMP recommends to collect the bleeding pattern and consumption data from treatment of at least 10 PTPs receiving on-demand treatment with turoctocog alfa for a minimum of 6 months in the ongoing study and to provide the results to the Agency after marketing authorisation.

There were no previously untreated patients included in the studies. There were also no haemostasis data for elderly patients. This missing information is included in the safety concerns in the RMP.

Risks

Unfavourable effects

There were no new or unexpected unfavourable effects found in Haemophilia A patients treated with turcoctocog alfa. The most commonly reported ADRs were increase in hepatic enzymes and injection site reaction.

Uncertainty in the knowledge about the unfavourable effects

No inhibitor development was detected in any patient treated with turoctocog alfa. Although the number of patients included in the database exceeds current guideline requirements, the safety database is relatively small in order to determine whether there is development of inhibitors and/or immunogenicity in patients treated with turoctocog alfa or whether there is a similar or even lower risk of developing inhibitors compared to other FVIII products. Inhibitor development was identified as an important identified risk and is being monitored through the RMP.

Benefit-risk balance

Importance of favourable and unfavourable effects

The clinical efficacy data was considered robust and suggests that the efficacy of turoctocog alfa is comparable to other FVIII products for the prevention and treatment of breakthrough bleedings and reaching haemostasis, including management of surgical interventions in previously treated patients suffering from Haemophilia A. Dosing of FVIII products is very individual and the recommended dosage information in the SmPC is based on clinical experience with other FVIII products and supported by the results from the clinical trials with turoctocog alfa. There is missing data for patients using on-demand treatment. However, this missing data does not affect the robustness of the efficacy data in the clinical study.

The safety database has sufficient number of patients across all clinical trials to evaluate the safety and tolerability of turoctocog alfa before marketing authorisation. The adverse events reported are considered similar to that reported for other licensed FVIII products. There were no patients that developed FVIII inhibitors and no thromboembolic events occurred until the cut-off date for serious adverse events (10 April 2013). The extension trial is on-going and will provide further data on serious adverse events, inhibitors and hypersensitivity reactions.

Benefit-risk balance

Based on the results of the pharmacokinetics studies NN7008-3522, NN7008-3893, NN7008-3600, NN7008-4015, pivotal study NN7008-3543, paediatric study NN7008-3545 and the extension trial NN7008-3568, the benefits of turoctocog alfa treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency) outweighed the adverse events (most commonly reported ADRs increase in hepatic enzymes and injection site reaction). Turoctocog alfa can be used for all age groups. Therefore, the CHMP considers that the benefit-risk balance for turoctocog alfa treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency) is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Novoeight in the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency) is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within eight months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

- **Additional risk minimisation measures**

Not applicable.

- **Obligation to complete post-authorisation measures**

Not applicable.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that Turoctocog alfa is qualified as a new active substance.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0150/2012 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.