Non-interventional study report

Study ID: NN7008-3553

A Multi-centre Non-interventional Study of Safety and Efficacy of turoctocog alfa (rFVIII) during Long-Term Treatment of Severe and Moderately Severe Haemophilia A (FVIII ≤2%)

guardian™5

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[redacted] [redacted] .

PASS information

Title	A multi-centre non-interventional study of safety and efficacy of turoctocog alfa (rFVIII) during long-term treatment of severe and moderately severe haemophilia A (FVIII ≤2%)
Version identifier of the final study report	2.0
Date of last version of the final study report	08 January 2021
EU PAS Register number	ENCEPP/SDPP/5501 EUPAS5501
EU PAS Register link	http://www.encepp.eu/encepp/viewResource.htm?id=12316
Active substance	Turoctocog alfa (human coagulation factor VIII (rDNA)) Antihaemorrhagics ATC code: [redacted]
Medicinal product	novoeight®/NovoEight®
Product reference	EU/1/13/888/001-006 FDA BLA application number: 125466
Procedure number	EMEA/H/C/002719
Marketing authorisation holder	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark
Joint PASS	No
Research question and objectives	The overall objective of the study is to provide additional documentation of the immunogenicity, and to obtain additional clinical data on turoctocog alfa in the setting of normal clinical practice. <u>Primary objective:</u> To assess the incidence rate of FVIII inhibitors during long-term prevention and treatment of bleeds with turoctocog alfa in previously FVIII treated patients with severe and moderately severe haemophilia A (FVIII ≤2%). <u>Secondary objective:</u> To further evaluate the general safety and obtain additional clinical experience of turoctocog alfa in prevention and treatment of bleeds and prevention of bleeds during and after surgery.
Countries of study	Austria, Czech Republic, France, Germany, Greece, Hungary, Italy, Netherlands, Poland, Slovakia, Slovenia, Switzerland, United States of America

Author	[redacted]
UTN	U1111-1126-0353
ClinicalTrials.gov identifier	NCT02035384
IND number	Not applicable
Generic name	Turoctocog alfa (human coagulation factor VIII (rDNA))
Indication	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). NovoEight® can be used for all age groups.
Physicians	There were 33 physicians appointed as individual overall responsible at the sites in the study. The following was appointed as the signatory physician for the study: [redacted]
Study sites	The patients were enrolled at 31 sites in 13 countries: Austria (1 site, 3 patients), Czech Republic (1 site, 1 patient), France (6 sites, 9 patients), Germany (6 sites, 11 patients), Greece (1 site, 3 patients), Hungary (2 sites, 2 patients), Italy (4 sites, 10 patients), Netherlands (2 sites, 14 patients), Poland (1 site, 6 patients), Slovenia (2 sites, 4 patients), Slovakia (2 sites, 3 patients), Switzerland (1 site, 1 patient) and United States of America (2 sites, 2 patients).
Study initiated	05 June 2014 (First patient first visit (FPFV))
Study completed	15 January 2020 (Last patient last visit (LPLV))

Marketing authorisation holder(s)

Marketing authorisation holder (MAH)	**Novo Nordisk A/S** Novo Allé DK-2880 Bagsvaerd Denmark
MAH contact person	[redacted] Novo Nordisk A/S Vandtårnsvej 108-110 DK-2860 Søborg

This study was conducted in accordance with the Declaration of Helsinki[1] and the Guidelines for Good Pharmacoepidemiology Practices.[2]

[redacted]

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List of in-text tables

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1 Abstract

Please refer to separate document.

2 List of abbreviations and definitions of terms

ABR	annualised bleeding rate
AESI	adverse event of special interest
AR	adverse reaction
BMI	body mass index
BU	bethesda units
CRF	case report form
DBL	database lock
ED	exposure day
EMA	European Medicines Agency
EnCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EOT	end of text
EU	European Union
FAS	full analysis set
FVIII	factor eight
GCP	Good clinical practice
GPP	Good pharmacoepidemiology practices
GVP	Good pharmacovigilance practice
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
IC	informed consent
ICF	informed consent form
IEC	independent ethics committee
IRB	institutional review board
LAR	legally authorised representative
MAH	marketing authorisation holder
MESI	medical event of special interest
NA	not applicable
NN	Novo Nordisk
NSR	non-interventional study report
PASS	post-authorisation safety study
PD	protocol deviations
PI	package insert
rFVIII	recombinant factor eight
SAR	serious adverse reaction
SAS	safety analysis set
SD	standard deviation
SmPC	summary of product characteristics
SOP	standard operation procedure
UTN	universal trial number

3 Physicians

The following investigator was designated as the principal physician for the study and was responsible for reviewing and approving the report:

- Prof. Dr [redacted]

Signature of the principal physician is provided in Annex 1, Document 16.1.5.

There were 33 physicians appointed as individual overall responsible at the sites in the study. A list of all physicians including coordinating physicians is provided in Annex 1, Document 16.1.4. The document further includes Curricula Vitae for each physician involved in the study.

4 Other responsible parties

This section is not applicable for this study.

5 Milestones

Table 5-1 Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	01 June 2014	05 June 2014	-
Registration in the EU PAS Register	13 January 2014	13 January 2014	-
End of data collection for interim report 1	05 December 2015	05 December 2015	18 months after the first patient data entry
Study progress report 1	01 June 2016	19 May 2016	-
Interim report 1	01 November 2016	20 October 2016	-
End of data collection for interim report 2	05 March 2018	01 March 2018	45 months after the first patient data entry
Interim report 2	05 October 2018	05 October 2018	-
End of data collection for final report	31 May 2021	15 January 2020	Actual end of data collection 15 January 2020
Final report of study results	04 October 2021	08 January 2021	Actual end of data collection 15 January 2020; Version 1.0 was finalised on 25 June 2020

The list of all IECs/IRBs (or other appropriate bodies as required locally) consulted in this study and the dates of approval for each site is provided in Annex 1, Document 16.1.3.

6 Rationale and background

6.1 Scientific background and rationale for study

Background

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. Haemophilia A occurs in approximately 1 in 5,000 live births. Classification of the severity of haemophilia A is based on plasma levels of FVIII, with patients <1% factor defined as severe; 1–5% as moderately severe; and 5-40% as mild.[3] Patients with haemophilia A lack or have a reduced production of FVIII, or they produce biochemically defective FVIII molecules. With a deficiency or absence of this factor, the activation of coagulation factor X becomes severely impaired, and consequently, the thrombin burst becomes delayed and insufficient for normal haemostasis. The haemostatic plug formed in these patients is therefore fragile and easily dissolved by normal fibrinolytic activity, leading to impaired haemostasis and prolonged bleeds.[4]

Recurrent bleeding in the same location, most commonly a weight-bearing joint, leads to chronic arthropathy, muscular atrophy and deformities. Treatment of bleeds as they manifest may delay this process, but does not prevent it.[5] For this reason, primary prophylaxis with regular FVIII injections in the non-bleeding state is a standard practice from early childhood. The primary goals of haemophilia therapy for patients are the prevention of bleeds, the rapid and definitive treatment of bleeds that do occur, and the provision of adequate haemostasis during surgery and other major challenges to haemostasis.

Turoctocog alfa is a recombinant FVIII (rFVIII) product intended for FVIII substitution therapy.

Rationale

Novo Nordisk has developed turoctocog alfa, a B-domain truncated human rFVIII for use in patients with haemophilia A.[6, 7] The guardian™5 study (hereafter referred to as NN7008-3553) is a non-interventional post-authorisation safety study (PASS) of recombinant human coagulation FVIII 'turoctocog alfa' (novoeight®, NovoEight®).

The major concern in the treatment of haemophilia A is the development of inhibitors against FVIII.[8] Inhibitors are antibodies formed as an immune response to allogeneic FVIII which reduce or eliminate the activity of FVIII. The presence of inhibitors neutralizes the effect of FVIII replacement therapy, resulting in increased risk of severe bleeding and development of debilitating haemophilic arthropathy and muscular atrophies, with severe consequences on quality-of-life for the patient.

The risk of developing inhibitors against FVIII is related to the mutation type in the FVIII gene,[9, 10] and possibly to other both genetic and non-genetic factors such as immunoregulatory genes, HLA-type, intensity of treatment, vaccinations or other challenges to the immune system.[11, 12] Inhibitor development in haemophilia A in most cases occurs during the early phases of replacement therapy, usually during the first 50 EDs.[13] In previously treated patients, inhibitors develop rarely, with an incidence of an approximate rate of 3 per 1000 patient years.[14] Switching to another FVIII product is not associated with increased incidence of inhibitor development.[15, 16] No

clear indication had been established that correlates development of inhibitor during initial period of switching of FVIII products.[15]

Data from the first human dose (23 patients) and PK trial (NN7008-3522) comparing turoctocog alfa and Advate® (octocog alfa) demonstrated comparable mean PK profile within the defined limits of comparability.[17]

Clinical experience included in the marketing application comprises phase 3 results from the pivotal (guardian™1 - NN7008-3543) and paediatric trials (guardian™3 - NN7008-3545) in patients with severe haemophilia A (FVIII <1%). In the guardian™1 trial, 146 adult and adolescent patients (>12 years) were followed during 75 EDs of preventive dosing with turoctocog alfa either 3 times weekly or every second day. Efficacy in bleeding prevention was demonstrated by a bleeding frequency clearly within the range expected during prophylaxis treatment in haemophilia A (mean annualised bleeding rate (ABR) of 6.5 bleeds/year). Spontaneous and traumatic bleeds during the trial were treated with a mean dose of 30.4 IU/kg (mean total dose used was 45.6 IU/kg until stop of bleed) and using a predefined four-point scale (Excellent, Good, Moderate or None), the haemostatic effect of turoctocog alfa was rated as 'Excellent' or 'Good' in 81% of all bleeds.

In the paediatric guardian™3 (NN7008-3545) trial, 63 previously treated patients <12 years of age (<6 years (n=31) and 6-11 years (n=32)) were dosed with turoctocog alfa and 60 patients completed 50 preventive EDs using a regimen similar to that in the adult/adolescent trial. The bleeding frequency was low with a mean ABR of 5.3 bleeds/year using a mean preventive dose of 36.8 IU/kg. Emergent bleeds in the trial were treated with a mean dose of 40.4 IU/kg (mean total dose of 50.2 IU/kg per bleed) and the haemostatic efficacy was rated as 'Excellent' or 'Good' in 92.1% of all bleeds. The number of infusions required to control a bleed was 1-2 in >95% of bleeds.

In the entire guardian™ clinical trial programme, 242 previously treated patients were exposed to turoctocog alfa for >50 EDs, and the total exposure exceeded 100,000 EDs. Despite regular testing and monitoring, no confirmed FVIII inhibitor or other safety concerns were detected within the trials in previously treated patients.

The European Medicines Agency (EMA) guideline for FVIII products points to the importance of ensuring consistency between the outcome from pre-authorisation clinical studies and from long-term routine use, thus mandating a post-marketing investigation if the development program does not include enough exposure days (EDs).[18] This is also in view of the limited availability of patients suffering from haemophilia A.

NN7008-3553 study was designed to provide additional documentation of the immunogenicity, safety and clinical efficacy of turoctocog alfa in normal clinical practice. The study was conducted in previously FVIII treated (>150 EDs) male patients with diagnosis of congenital severe and moderately severe haemophilia A (FVIII ≤2%) in line with EMA guideline.[19] The emphasis was to place an evidence of FVIII inhibitors, adverse reactions (ARs) and efficacy. Clinical efficacy was assessed by evaluation of the haemostatic effect, ABR and consumption of turoctocog alfa.

6.2 Ethics

The study was conducted in accordance with Declaration of Helsinki[1], the Guidelines for Good Pharmacepidemiology Practices (GPP)[2] and Good Pharmacovigilance Practice (GVP).[20]

The 21 Code of Federal Regulations, parts 312, 50, and 56 were followed.

Prior to study initiation, the protocol, any amendments, patient information/informed consent form and any other written information to be provided to the patient and patient enrolment procedures were reviewed and approved by an independent ethics committee (IEC)/institutional review board (IRB) (or other appropriate bodies as required locally). The IECs/IRBs were transparent in their functioning, independent of the researcher, the sponsor and any other undue influence, and duly qualified.

A list of the IECs/IRBs (or other appropriate bodies as required locally) that reviewed and approved the protocol, protocol amendments and patient information/informed consent form, including approval dates, is provided in Annex 1, Document 16.1.3.

6.3 Patient information/informed consent form

Prior to any study-related activity, the physician provided the patient and/or the patient's legally authorised representative (LAR) oral and written information about the study in a form that the patient or the patient's LAR could read and understand. This includes the use of impartial witness where required. In this study the notion of legal representative should be understood as either parents, or LAR, as defined in Member States' national laws, who consents on behalf of the child.

A voluntary, signed and personally dated informed consent (IC) form was to be obtained from patient and/or the patient's parent(s) or LAR prior to any study-related activities.

In obtaining and documenting IC, the physician complied with the applicable regulatory requirement(s) and adhered to the requirements in the Declaration of Helsinki.[1]

The task of seeking IC was to be performed by the physician or another medically qualified person delegated by the physician, if permitted by local regulation, who should sign and date the patient information/informed consent form. The physician was to inform the patient and/or patients parents/LAR in a timely manner of any new information arising during the study that could affect the patient's willingness to continue in the study. In this case, a revised written patient information was to be provided and a new IC was to be obtained.

Children, incapable of giving consent, were included as patients in this study in accordance with Health Authority guidelines for development of FVIII products.[19]

Consent: As a child is unable to provide legally binding consent, IC was to be obtained from the parents/LAR on the child's behalf. The specific and written IC of the parents/LAR was to be obtained prior to enrolling a child in the study.

Assent: It was expected that the physician would offer the child opportunity to give assent to decisions about participation in the study in addition to obtaining consent from parents/LAR according to local requirements. An "assent form" was to be provided and used whenever a child was deemed capable of forming an opinion and assessing the implications of his/her decisions.

The requirement for obtaining IC from a patient's LAR was that the patient was unable to provide IC, and the process has been approved by the relevant IRB/IEC.

An IC form for the male patient's female partner was to be signed before collecting any data from the patient's female partners i.e. in case of pregnancy.

The physician retained the consent forms. The consent forms were available to Novo Nordisk for inspection. The master patient information/informed consent form is available in Annex 1, Document 16.1.3.

Appropriate measures such as encryption or deletion were enforced to protect the identity of patients when transmitting data, in all presentations and publications, as required by local/regional/national requirements.

6.3.1 Informed consent for genotype testing

Patients/parents or LAR were asked if available result(s) of previous FVIII genotype test(s) or result from a genotype test performed during the patient's participation in the study could be documented. If agreed to, this was to be documented on a separate page in the IC form.

7 Research question and objectives

The overall objective of the study is to provide additional documentation of the immunogenicity, and to obtain additional clinical data on turoctocog alfa in the setting of normal clinical practice.

As stated in the protocol and amendments (included in Annex 1, Document 16.1.1), the objectives of the study were as follows:

Primary objective:

- The primary objective is to assess the incidence rate of FVIII inhibitors (≥0.6 BU for central laboratory analyses, or above the specific local laboratory reference range) during long-term prevention and treatment of bleeds with turoctocog alfa in previously FVIII treated (>150 EDs) patients with severe and moderately severe haemophilia A (FVIII ≤2%).

Secondary objective:

- To further evaluate the general safety and obtain additional clinical experience of turoctocog alfa in prevention and treatment of bleeds and prevention of bleeds during and after surgery.

8 Amendments and updates

There were 4 amendments to the study protocol after the start of data collection in this study.

Table 8-1 Amendments to the protocol

Date	Sections of study protocol	Amendment or update and Reason
29 September 2014 (amendment no. 1)	NA	Local amendment, only applicable in France
22 September 2015 (amendment no. 2)	1, 2, 3, 4, 5, 6, 7, 9 & 11	The present guardian™5 recruitment status is significantly below planned target. The main reason for the low recruitment is the protocol inclusion criteria requiring that patients should be turoctocog alfa naïve i.e. "No previous exposure to turoctocog alfa". Therefore, patients have to consent to the study before receiving their first dosage. Most sites are reluctant to commit to study participation until they have started to prescribe turoctocog alfa. As the switch to turoctocog alfa for the majority of patients usually occur within the initial period (first three months) after launch of turoctocog alfa in each country, the availability of eligible patients has already dropped significantly by the time sites have agreed to participate. The 'Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products' requires study patients to be free from inhibitors at inclusion, but do not require patients to be naïve. Requiring no previous participation in turoctocog alfa studies is therefore sufficient to ensure that only patients who are new to turoctocog alfa will join this non-interventional study. To minimise the chance of deselection of patients who have developed inhibitors in the period between switching to turoctocog alfa and study inclusion, patients with clinical suspicion of inhibitors will be eligible, but only if they do not have a history of inhibitors on previous FVIII products and if a negative inhibitor test has been obtained prior to first dosing (sampled within four weeks prior to first dosing) with turoctocog alfa. In this way selection bias with regards to patients that may have developed inhibitors to turoctocog alfa prior to study inclusion will be avoided. Patients receiving other FVIII products after the first dosing with turoctocog alfa should also be excluded to ensure that development of an inhibitor can be directly linked to turoctocog alfa.
06 January 2016 (amendment no. 3)	2, 6, 9.7.2 & 12.3	According to the European Medicine Agency Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (dated 21 July 2011) a separate progress study report should be provided to the relevant competent authority(ies) 2 years after the start of the post-marketing investigation. Study protocol version 5.0 dated 22 September 2015 section 6 Milestones list that an interim report is planned at 2 years after study start. Additionally, protocol section 6 Milestones and protocol section 12.3 Progress reports and final report does not mention that a progress report will be provided to the relevant competent authorities 2 years after the start of the study. Accordingly, the rationale for this amendment is to state that a separate progress report is to be provided to the relevant competent authorities 2 years after the study start and to amend the planned timelines for the interim study report.

Date	Sections of study protocol	Amendment or update and Reason
13 January 2017 (amendment no. 4)	1, 2, 4, 5, 6, 9.1.1, 9.2.4, Table 9.1, 9.3.1.1, 9.3.1.2, 9.3.1.3, 9.3.3.4, 9.3.3.5, previous 9.3.3.8, previous 9.3.3.9, 9.3.4.6, 9.3.4.9, 9.7.2, 9.7.3, 9.7.4, 9.7.5, 10.1	The present guardian™5 recruitment status is significantly below planned target. The timelines have been changed according to the current enrolment rate within the study. The aim of this study is to collect real life data for NovoEight® treatment. To be able to fulfil this aim, withdrawal criteria no. 1, no. 2 and no. 3 have been deleted, in order to avoid bias within the collected data. A new withdrawal criterion no. 4 has been created. The changes in the withdrawal criteria also results in a change in the concomitant medication section (9.3.4.6), where allowed and prohibited medications have been deleted. Changes are required to the End of Study procedure to get as much data as possible in after 50 patients have reached a minimum of 100 EDs. Specific laboratory analyses in data collected for haematology, biochemistry and viral antibody information are not done within this study. Therefore, it was decided to delete collection for haematology, biochemistry and viral antibody information for all visits from the protocol. Only HIV status and T cell subset CD4+ data will be collected at visit 1 to verify inclusion criteria no. 7 for HIV positive patients. For all further visits T cell subset: CD4+ will also be deleted. This amendment also includes minor changes to the layout and wording within the flow chart. The name of the main author and the Marketing Authorisation Holder (MAH) were adapted within the whole protocol. The separated sections of change will not be listed in the amendment. The term Medical Event of Special Interest (MESI) has been updated to Adverse Event of Special Interest (AESI) within the whole protocol to follow the term according to our current Standard Operation Procedure (SOP). The separated sections of change was not listed in the amendment.

9 Research methods

9.1 Study design

This was a prospective, multinational, non-randomised, non-interventional PASS in previously FVIII treated (>150 EDs) male patients with severe and moderately severe haemophilia A with FVIII ≤2%. Only patients for whom it had already been decided to start treatment or had already started treatment with commercially available turoctocog alfa and who did not previously participate in any clinical trials with turoctocog alfa were eligible for the study.

Patients with FVIII between 1 and 2% were classified as moderately severe haemophilia A, but most often required treatment due to bleeding tendency. Inclusion of these patients in the study was in accordance with the EMA guideline for a post-marketing investigation for rFVIII products.[19] This patient group was also part of the population intended for treatment with turoctocog alfa. For study size and age distribution, refer to Section 9.7. This study was planned to observe at least 50 patients for a minimum of 100 EDs to study product after inclusion in the study. The study duration was estimated to be 7 years with a planned recruitment period of 70 months.

For each patient, data was planned to be collected:

- until the patient reached a minimum of 100* EDs with turoctocog alfa after inclusion in the study **or**
- until at least 50 patients have a minimum of 100* EDs with turoctocog alfa after inclusion in the study

whichever came first.

*the 100 EDs were counted from the baseline visit (visit 1).

One (1) ED is defined as each day a patient is administered turoctocog alfa and a ‘day’ is implicit a ‘calendar day’. Several doses with turoctocog alfa within the same calendar day would be recorded as 1 ED.

No controls or blinding procedures were applied. There was no dispensing of any study product as part of this study. All direction for study product usage (prophylactic as well as on-demand) was solely at the discretion of the physician in accordance with clinical daily practice and preferably in accordance with the approved product label (US Package insert (PI), European Summary of Product Characteristics (SmPC) or corresponding local prescribing information).

The physician was encouraged to perform clinical evaluation and blood testing for FVIII inhibitors as a routine practice during visits to the clinic and also when there was lack of therapeutic effect in accordance with the product labelling. Patients who developed inhibitors could continue treatment with turoctocog alfa and study participation. If this was the case, the dosing and dosing frequency was to be decided by the treating physician based on clinical evaluation.

The study design was in accordance with EMA guideline from July 2011[19] for post-marketing investigations of rFVIII products. The multi-centre, multi-national design was chosen to ensure a sufficient patient pool and relevant ethnic diversity of haemophilia A patients, as turoctocog alfa is marketed globally.

An active comparator was not chosen as extensive comparative data from recently registered rFVIII products are available in comparable global populations including patients from EU and US.[21, 22]

Endpoints

Primary endpoint

- Incidence rate of FVIII inhibitors (≥0.6 BU for central laboratory analyses, or above the specific local laboratory reference range) represented as the percentage of patients developing inhibitors

Secondary endpoints

- Safety endpoints
  - Number of adverse reactions (ARs) reported during the study period
  - Number of serious adverse reactions (SARs) reported during the study period

- Efficacy endpoints
  - Haemostatic effect of turoctocog alfa in the treatment of bleeds as assessed by the patient or the physician according to a predefined four point scale: excellent, good, moderate, or none
  - Haemostatic effect of turoctocog alfa during surgical procedures as assessed by evaluation according to a predefined four point scale: excellent, good, moderate, or none
  - Annualised bleeding rate for patients using turoctocog alfa for preventive treatment
  - Annualised bleeding rate for patients using turoctocog alfa for on-demand treatment
  - Total consumption of turoctocog alfa per patient (prevention, treatment of bleeds and surgery) per month
  - Actual consumption of turoctocog alfa (IU/kg BW/months) for prevention
  - Actual consumption of turoctocog alfa per bleed (IU/kg BW/bleeding episode)
  - Actual consumption of turoctocog alfa (IU/kg BW) from the day of surgery until the day of return to preventive regimen

9.2 Setting

Patients obtained routine medical care with turoctocog alfa at their respective clinics in accordance with local practices. All study visits were performed according to the local clinical practice. No additional visits were conducted due to the participation in this study.

Clinical evaluation was carried out by the physician as specified in Table 9-1. The dosing and dosing frequency was to be decided by the physician based on clinical evaluation. Patient identification was accomplished via allocation of a 6 digit number which consisted of a 3 digit site code and a 3 digit patient ID. Numbers were provided by Novo Nordisk.

Signed informed consent was to be obtained prior to any study related activities.

Patients enrolled in the study were to be provided with contact address(es) and telephone number(s) of the physician site and/or staff. During a patient's participation in the study, all relevant data were to be entered in the paper case report form (CRF). In case a patient was prematurely withdrawn from the study, the physician was expected to ensure that the procedures for the last visit were

recorded. The primary reason (e.g. adverse reaction or other) for discontinuation was to be specified in the paper CRF.

For more information on visit procedures, see Annex 1, Document 16.1.1, Protocol Section 9.3.1.

Table 9-1 Flow chart

Visit number	Baseline (Visit 1)	Assessment visits (Visit 2.1, 2.2, 2.3)	End of study (Visit 3)
Visit window[1]		**0 - 99 EDs**	**≥100[2] EDs**
PATIENT RELATED INFO / ASSESSMENTS[3]			
Informed consent	●		
Consent to report FVIII genotype result	●		
Inclusion/Exclusion Criteria	●		
Withdrawal Criteria	●	●	●
Haemophilia treatment history	●		
Concomitant illnesses	●		
Medical history	●		
Concomitant medication	●	●	●
Demography	●		
Body measurements	●	●	●
FVIII genotype	●[4]	●[5]	●[5]
Details of haemophilia	●		
Family history of haemophilia	●		
EFFICACY[3]			
Bleed(s)		●	●
Surgery	●	●	●
SAFETY			
Adverse reactions	●	●	●
Physical examination	●	●	●
Vital signs	●	●	●
FVIII recovery	●	●	●
FVIII trough level	●	●	●
FVIII inhibitors	●[6]	●[6]	●[6]
OTHER ASSESSMENTS			
HIV status	●[7]		
T cells subset: CD4+	●[8]		
STUDY MATERIAL			
Administration of turoctocog alfa	●	●	●
Diary dispensing and/or collection	●	●	●
Review of patient diary data		●	●
End of Study form			●

[1]For patients with on-demand treatment, the time period between visits was recommended not to exceed 6 months

[2]100 EDs with turoctocog alfa after inclusion in the study

[redacted]

[3]In this non-interventional study, only results from assessments performed according to local clinical practice was to be recorded. However, adverse reactions (ARs) were always to be assessed and reported

[4]An available genotype result was to be documented if consented to by the patient/LAR

[5]If a genotype test was performed during the study, the result was to be documented, if consented to by the patient/LAR.

[6]A 48 hours washout period was recommended

[7]If assessment was performed. The results could be transferred from medical records, if available

[8]If HIV positive, last value of CD4+ T-cells dated no more than 6 months prior to study entry.

9.3 Patients

The below listed numbers represent the planned number of patients:

- Planned number of patients to be included (baseline screening): Approx. 80
- Planned number of patients to be included in the study: Approx. 70
- Planned number of patients to complete the study: Approx. 50
- Anticipated number of patients to be included in each country: Approx. 5-8

9.3.1 Inclusion criteria

For an eligible patient, all inclusion criteria were to be answered "yes".

1. Informed consent obtained before any study-related activities. Study-related activities are any procedure related to recording of data according to the protocol.
2. Previously FVIII treated (>150 EDs at the time of first dosing with turoctocog alfa) male patients with the diagnosis of congenital severe and moderately severe haemophilia A (FVIII ≤2%).
3. The decision to initiate treatment with commercially available turoctocog alfa has been made by the patient/parent and the patient's treating physician before and independently from the decision to include the patient in this study.
4. Availability of a detailed and reliable patient documentation (patient records, diary, logbook etc.) covering either the last 50 EDs or the last 2 years per patient to confirm treatment modality (i.e. prophylaxis, on-demand or recent surgery) prior to enrolment.
5. A negative FVIII inhibitor test obtained not more than four weeks prior to first dosing with turoctocog alfa.
6. Patients with a history of FVIII inhibitors and who have been immune-tolerized to FVIII through Immune Tolerance Induction treatment must have FVIII plasma recovery level ≥66% of expected level and a FVIII half- life ($T_{½}$) of ≥6 h after a 72 h wash-out period (as demonstrated by available medical records).
7. No clinical suspicion of HIV-1 or, if HIV-1 seropositive, viral load <400.000 copies/mL and immunocompetent with CD4+ lymphocyte count ≥200/µL, as assessed during the last 6 months prior to the baseline visit.

9.3.2 Exclusion criteria

For an eligible patient, all exclusion criteria were to be answered "no".

1. Contraindications for use according to the approved product information text (US Package Insert (PI), European Summary of Product Characteristics (SmPC) or corresponding local prescribing information). This includes known or suspected allergy to turoctocog alfa or related products.

2. Previous participation and/or withdrawal from this study. Participation is defined as having given informed consent in this study.
3. Treatment with any investigational drug within 30 days prior to enrolment into the study.
4. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation.
5. Previous participation in any clinical trial with turoctocog alfa.
6. Treatment with other FVIII products after initiation of treatment with turoctocog alfa.

9.3.3 Removal of patients from therapy or assessment

The patient could withdraw at will at any time. The legally responsible person for the patient could withdraw the child from the study at will at any time.

The patient could be withdrawn from the study at the discretion of the physician or the sponsor due to a safety concern.

Patients were to be withdrawn from the study if started regular treatment with another FVIII products other than turoctocog alfa after initiation of study product treatment within this study.

9.3.4 Sources of patients

The study population were the patients who, based on the indication, would benefit from treatment with turoctocog alfa. For this non-interventional study, the prospective patients were to be identified amongst those patients for whom it had already been decided that they would switch to turoctocog alfa. As a multi-centre, multinational population was selected, the generalisability of the study is evaluated as high. The study being global, patients from different ethnicities were required to be included.

The study population characterised through the inclusion criteria:

- Criterion no. 1 was included in accordance with Good Pharmacoepidemiology Practice (GPP)[2]
- Criteria nos. 2, 4, 6 and 7 were derived from the EMA guidelines concerning post-marketing investigation of recombinant and human plasma-derived FVIII products[19]
- Criterion no. 3 ensured that patients were not prescribed turoctocog alfa because of study participation
- Criterion no. 5 was derived from the World Federation of Haemophilia guidelines for the management of haemophilia[23] and from the EMA guidelines concerning post-marketing investigation of recombinant and human plasma-derived FVIII products[19]

The study population characterised through the exclusion criteria:

- Criterion no. 1 was a prerequisite for a non-interventional study
- Criteria no. 2 was included to ensure that a patient only counts once in the data analyses
- Criterion no. 3 was selected to minimise any effect of other investigational compounds on the patient's coagulation and immune system
- Criterion no. 4 was included to ensure adequate study understanding and cooperation
- Criterion no. 5 was included to avoid inclusion of patients that have been treated with turoctocog alfa for a long time (i.e. in the extension study)

- Criterion no. 6 was derived from the World Federation of Haemophilia guidelines for the management of haemophilia[23] and from the EMA guidelines concerning post-marketing investigation of recombinant and human plasma-derived FVIII products[19]

The eligibility criteria are considered to allow inclusion of most patients with severe and moderately severe haemophilia A (FVIII ≤2%) and did not impose any significant limitations in the number of patients available for analysis.

9.3.5 Methods of selection of patients

Patients were identified by treating physician and included in the study based on the inclusion and exclusion criteria, see Section 9.3.1 and 9.3.2.

9.4 Variables

The study was designed to observe routine treatment of the individual patient. Data and results from assessments and laboratory sampling performed according to clinical practice at the participating sites were to be recorded upon availability.

The physician was encouraged to perform assessments and blood sampling at all visits according to local clinical practice, if applicable.

9.4.1 Efficacy variables

Bleeding episodes

For bleeds the following were to be recorded in patient's diary and paper CRF:

- Date and time of onset of bleeding episode
- Treatment of bleeding episode
- Location of the bleed (specify location e.g. joint, muscular etc.)
- Type of bleed (spontaneous, traumatic)
- Haemostatic drug used for treatment
- Dose level(s), strength(s) and time(s) of administration
- Other therapy used (compression, ice or other)
- Date and time of stop of bleeding episode
- Severity of the bleed (Mild/Moderate or Severe)
- Clinical evaluation of the haemostatic response (Excellent, Good, Moderate or None)

9.4.2 Safety variables

- Adverse reactions
- Physical examination
- Vital signs
- Laboratory tests
  - FVIII inhibitor testing
  - FVIII recovery
  - FVIII trough level
  - HIV status and T-cells sub-set

9.4.3 Other variables

- Demography
- Body measurement
- FVIII genotype
- Haemophilia treatment history
- Concomitant illness and Medical history
- Concomitant medication
- Haemophilia details
- Family history of haemophilia
- Diary
- Study product

Refer to the study protocol for details on assessments for efficacy (Annex 1, Document 16.1.1, Protocol Section 9.3.2), assessments for safety (Annex 1, Document 16.1.1, Protocol Section 9.3.3) and other assessments (Annex 1, Document 16.1.1, Protocol Section 9.3.4). For safety definitions, refer to the Annex 1, Document 16.1.1, Protocol Section 11.2.

9.5 Data sources and measurement

The intention of this non-interventional study was to observe routine treatment of the individual patient. Data and results available in patient's medical record from assessments and laboratory sampling (performed according to clinical practice at the participating sites) were to be recorded in the paper CRF. For more detail, refer to Section 9.2 for study settings and Table 9-1 for study flow chart. Information related to treatment and bleeding episodes were to be captured in a patient diary by the patient or parent/caregiver. In case a patient was unable to enter a treatment or bleeding episode in the diary, or was hospitalised, it was to be reported in the patient record and subsequently in the paper CRF by the physician.

Novo Nordisk provided the paper CRFs. Paper CRF entries were to be printed legibly using a ballpoint pen. For further details on the paper CRF, refer to
Annex 1, Document 16.1.1, Protocol Section 9.6.2.

9.6 Bias

As this was a non-interventional PASS, there would be a number of potential confounding factors, which are controlled in randomised clinical trials. This involved selection bias of patients in relation to the willingness or ability to cooperate in a study like the non-interventional PASS with a diary. In addition, the use of a patient diary introduced an increased risk of incorrect recording of the administered dose and bleed severity evaluation. This was minimised by review of the diary by the physician before entering data into the CRF. Concerning the issues of haemostatic effect evaluation[24] during home treatment, the risk of misclassification was especially relevant. To minimise misclassification, the patient and the physician evaluated the diary recordings related to the bleeding episodes together at the next visit, before data was entered into the CRF. Medical

consistency checks by qualified medical persons to capture and resolve inconsistencies were performed.

9.7 Study size

Sample size was based on regulatory (EMA) requirements.[19] According to the EMA guideline for rFVIII products[19] data from at least 200 patients with 100 EDs are required. At least 30% of these patients are required to be <12 years of age, corresponding to 60 patients.

A total of 167 patients in the guardian™2 (NN7008-3568) trial had already accomplished 100 EDs (as of 28 August 2012); out of these 53 were children.

Based on this, the sample size for the study was minimum 50 previously FVIII treated patients who had not previously taken part in any guardian™ clinical trials and of which at least 10 patients (20%) were required to be <12 years old at time of enrolment.

9.8 Data transformation

The patient and the biological material obtained from the patient was identified by a patient number, study site, and study ID number. Appropriate measures such as encryption or deletion were required to be enforced to protect the identity of human subjects in all presentations and publications as required by local/regional/national requirements. Appropriate measures such as encryption of data files were to be used to assure confidentiality of patient data when it was transmitted over open networks. Laboratory data was transferred electronically from the Central Laboratory performing clinical analyses. The electronic laboratory data was considered as the source data. In cases where laboratory data was transferred via non-secure electronic networks, data was to be encrypted during transfer.

9.9 Statistical methods

No formal testing of statistical hypotheses was performed. Evaluation of data was based upon descriptive statistics, i.e. summary tables, listings, and figures. All main descriptions and evaluation of safety and efficacy data was based on the full analysis set (FAS). The FAS included all dosed patients with data after dosing, except those patients who had received a positive inhibitor test result after inclusion in the study for a test performed prior to first dose of turoctocog alfa. These patients were to be listed separately. The safety analysis set (SAS) was identical to the FAS.

No formal per-protocol analysis was planned. However, the sensibility of the results with respect to single patient's data could be investigated by performing additional analyses on subsets of data.

9.9.1 Main summary measures

All summaries demonstrated the results for the full group of patients and for the subgroups of patients with endogenous FVIII level <1% and 1-2% at inclusion, as well as for the subgroups of patients <12 years and ≥12 years of age. Categorical data were summarised by frequency tables while continuous data were summarised by mean, standard deviation, minimum and maximum value.

9.9.2 Main statistical methods

9.9.2.1 Primary endpoint

Primary endpoint was the incidence rate of FVIII inhibitors (≥0.6 BU for central laboratory analyses or above the specific local laboratory reference range) represented as the percentage of patients developing inhibitors.

Primary analysis

The incidence rate of FVIII inhibitors was calculated and represented as the percentage of patients developing inhibitors and a 1-sided 97.5% upper confidence limit was provided based on an exact calculation for a binomial distribution. In the analysis, all patients with at least one inhibitor test performed after baseline visit were included. For the calculation of the incidence rate, the numerator included all patients with inhibitors confirmed by laboratory, except those patients who had received a positive inhibitor test result after inclusion in the study for a test performed prior to the first dose of turoctocog alfa. The denominator included all patients in the study who were exposed to turoctocog alfa, except those patients who had received a positive inhibitor test result after inclusion in the study for a test performed prior to first dose of turoctocog alfa, these patients were to be listed separately.

Other analyses

In addition to the primary analysis, the time to inhibitor development was presented by Kaplan Meier plot, where the time scale was defined as EDs. Furthermore, an annualised rate of inhibitors per patient year was calculated using a Poisson model allowing for over-dispersion with a log-link function and the logarithm of the time spent in the study as offset, if appropriate.

Presentation

Analyses and presentations of the primary endpoint were made for each treatment regimen (preventive treatment or on-demand treatment) and for all patients, and furthermore for each patient subgroup (age at inclusion, severity of Haemophilia A: severe, moderately severe).

9.9.2.2 Secondary endpoints

Secondary effectiveness endpoints

The secondary effectiveness endpoints were reported to obtain additional clinical experience of turoctocog alfa in prevention and treatment of bleeds and prevention of bleeds during and after surgery. Refer to Section 9.1 for secondary efficacy endpoints.

Analyses and presentation

- All efficacy endpoints were summarised and listed.
- Treatment success was summarised by counting ‘Good’ or ‘Excellent’ as ‘success’; and ‘None’ and ‘Moderate’ as ‘failure’. Bleeding episodes with missing response were counted as treatment failure in the sensitivity analysis (see Section 9.9.4).
- The ABR was analysed by a negative binomial model and estimated ABR with confidence interval (CI) was presented.

Secondary safety endpoints

Refer to Section 9.1 for secondary safety endpoints.

Analyses and presentation

All adverse reactions and serious adverse reactions reported during the study were to be summarised by number of reactions and number of patients with any reaction. Since patients had different durations in the study, adverse reaction rates (reactions per 100 patient years of exposure) were also to be calculated and presented. The summaries of adverse reactions and serious adverse reactions were also to be presented by severity and by type of regimen.

Furthermore, the listings were provided displaying all adverse reactions, serious adverse reactions and adverse event of special interests (AESIs) reported during the study including pertinent clinical information.

9.9.3 Missing values

Due to the observational nature of the study, data and results from assessments and laboratory sampling were performed according to the local clinical practice and were recorded upon availability.

There were certain amount of missing data in the CRF and diaries due to:

- limited on-site monitoring to ensure the transfer of clinical data from medical records into the CRF
- assessment schedule followed the local clinical practice, which led to variation between sites and countries
- patients were allowed to use their own diary for recording of bleeding episodes, which did not always capture the same information as the Novo Nordisk (NN) diary
- patients who did not maintain the diary were not discontinued.

Notably, for some patients inhibitor test results were not available at all the visits, and for several patients no inhibitor test result was available post-baseline.

The risk time for each patient was counted from the date of signing informed consent to the day the patient left the study, which was reflected in the denominator of the associated rates. For bleeding rate and consumption calculation, if the patient had lost or not filled in the diary during a specific period, then this period was not counted as risk time. However, adverse reactions were reported directly to sites outside the diary tool, and therefore missing diary periods were counted as risk time for adverse reactions.

For patients who had not used the diary provided by Novo Nordisk and the haemostatic effect was not captured for any episodes, the patient ID was documented in the DBL minutes. Such patients were excluded from the secondary efficacy endpoint analysis of haemostatic effect.

9.9.4 Sensitivity analyses

A Poisson model with over-dispersion was applied in the sensitivity analysis of ABR (secondary efficacy endpoint).

The analysis of the secondary endpoint of the haemostatic effect was repeated with the inclusion of non-systematic missing responses as a sensitivity analysis assuming these responses were missing at random.

No other sensitivity analyses were performed.

9.9.5 Amendments to the statistical analysis plan

The interim cut-off date for the second interim analysis defined in the protocol was updated from 35 months stated in Annex 1, Document 16.1.1, Protocol Section 9.7.2 to 45 months in alignment with the milestone dates described in Section 5.

All data from the date of signing informed consent were collected and analysed. Number of exposure days were counted from the date of signing inform consent instead of the date of the baseline visit as stated in the protocol.

The analysis of the primary endpoint (incidence rate of FVIII inhibitors) was not performed for the subgroup of patients with surgery/invasive procedures due to the relative low reporting of surgeries and since no incidences of inhibitors were reported, this does not change any conclusions.

9.9.5.1 Additional analysis

Following additional analysis were conducted and/or presented in addition to the endpoints mentioned in Section 9.9.2.

- Annualised bleeding rate for patients on prophylaxis regimen by cause of bleeding (spontaneous or traumatic) was analysed by a negative binomial model and estimated ABR with confidence interval (CI) was presented.
- The number of injections of turoctocog alfa per bleeding episode was calculated as the number of injections of turoctocog alfa used in the time period from start to stop of the bleed.
- The average number of bleeds per year for haemophilia history was calculated and presented along with the average number of bleeds per month.
- A listing of patients with clinical suspicion of positive inhibitors at baseline was presented.

9.10 Quality control

During the course of the study, the monitor was to visit the study site at intervals specified in the monitoring guideline for the study. The purpose of these visits was to ensure that the protocol was adhered to, that all issues and data were recorded and to collect completed paper CRF pages. The extent of source data verification and validation of endpoints were described in the monitoring guideline for the study. The monitor ensured that the paper CRFs were completed and collected. Refer to Annex 1, Document 16.1.1, Protocol Section 9.8 for quality control.

10 Results

10.1 Participants

A total of 70 patients were screened, of which 1 patient was a screen failure (Annex 2, Document 16.2.1, Listing 16.2.1.1) and 69 patients were included in the study (Table 10-2). Of the 69 patients, 1 patient with FVIII level >2% at inclusion could not be classified into "severe haemophilia (FVIII level <1%) " or "moderately severe haemophilia (FVIII level 1-2%)" categories; however, this patient is included in the total number of patients in the analyses by severity of haemophilia A to represent the FAS (Table 10-1).

Please note, the results are presented for all the patients and for the subgroups of patients by age (<12 years and ≥12 years) at inclusion as well as by haemophilia severity (severe haemophilia and moderately severe haemophilia) at inclusion. Number of patients in each subgroup are presented in Table 10-1.

Table 10-1 Number of patients in each subgroup by age group and by severity of Haemophilia A at inclusion - all patients

Subgroups	N (%)
By age group	**69 (100.0)**
<12 years of age	14 (20.3)
≥12 years of age	55 (79.7)
By severity of Haemophilia A*	**69 (100.0)**
Severe haemophilia (FVIII level <1%)	58 (84.1)
Moderately severe haemophilia (FVIII level 1-2%)	10 (14.5)

N: Number of patients, %: Percentage of patients

*For 1 patient, after treatment initiation, it was noted that the FVIII level at inclusion was >2%. This patient is included in the total number of patients in the analyses by severity of Haemophilia A to represent the full analysis set. The severity is marked as 'unknown' for this patient in the listings.

Cross-reference: based on EOT Tables 14.2.1 and 14.2.2

Of the 69 enrolled patients, 11 patients (15.9%) were withdrawn from the study. These included 8 patients with severe haemophilia (4 patients ≥12 years and 4 patients <12 years) and 3 patients with moderately severe haemophilia (2 patients ≥12 years and 1 patient <12 years) (Table 10-2 and Annex 2, Document 16.2.1, Listing 16.2.1.2).

Of the 11 withdrawn patients, 6 patients withdrew consent and 5 patients were withdrawn by the physician (all (5) patients due to lack of availability of study product; and among them, 1 patient had protocol violation, which led to discontinuation). Of the 6 patients who withdrew consent, 2 patients wanted to switch to another product, 2 patients withdrew due to personal reasons [redacted]), 1 patient forgot the diary and did not want to continue, and for 1 patient the reason of withdrawal was not available (EOT Table 14.2.4 and Annex 2, Document 16.2.1, Listing 16.2.1.2).

[redacted]

Patients who violated inclusion and exclusion criteria are listed in Annex 2, Document 16.2.1, Listing 16.2.1.3 and Listing 16.2.1.4.

Among the 11 withdrawn patients:

- One (1) patient withdrew before being dosed and was therefore excluded from the FAS. The patient forgot diary and did not want to continue the study
- Two (2) patients withdrew approximately 7 months after enrolment into the study and 7 months post first dose of turoctocog alfa
- Two (2) patients withdrew approximately 5 months after enrolment into the study; of these 1 patient withdrew post 1.5 months and another patient withdrew post 5 months of first dose of turoctocog alfa
- Two (2) patient withdrew approximately 4 months after enrolment into the study and 4 months post first dose of turoctocog alfa
- One (1) patient withdrew approximately 15 months after enrolment into the study and 2 months post first dose of turoctocog alfa
- One (1) patient withdrew approximately 11 months after enrolment into the study and 11 months post first dose of turoctocog alfa
- One (1) patient withdrew approximately 6 months after enrolment into the study and 6 months post first dose of turoctocog alfa
- One (1) patient withdrew approximately 2.5 months after enrolment into the study and 2.5 months post first dose of turoctocog alfa

(Annex 2, Document 16.2.3, Listing 16.2.3.1, Annex 2, Document 16.2.4, Listing 16.2.4.2 and Annex 2, Document 16.2.5, Listing 16.2.5.1).

Of the 69 enrolled patients, 68 patients were exposed to turoctocog alfa, constituting the FAS and SAS. These 68 patients were exposed to turoctocog alfa for a total of 87.8 patient years and 8967 EDs (Table 10-2). The total mean EDs (including all EDs for prophylaxis regimen, treatment of bleed or surgery) per patient was 131.9 (range: 7.0-766.0) (Table 10-3).

Of the 68 exposed patients, 63 patients were on prophylaxis regimen (14 patients <12 years and 49 patients ≥12 years) and 5 patients were on on-demand regimen (all patients ≥12 years) (Table 10-2).

A total of 58 (84.1%) patients (9 patients <12 years and 49 patients ≥12 years) completed the study, of which 8 patients (all ≥12 years) were considered as study completers without reaching a minimum of 100 EDs by the physician (Table 10-2 and EOT Table 14.2.3).

A total of 8 patients undergone 11 surgeries, [redacted] (Table 10-2 and Annex 2, Document 16.2.6, Listing 16.2.6.2).

Patient disposition by age and by haemophilia severity at inclusion is presented in Table 10-2.

Informed consent details for individual patients are listed in Annex 2, Document 16.2.4, Listing 16.2.4.1. Visit dates are listed in Annex 2, Document 16.2.4, Listing 16.2.4.2.

Table 10-2 Patient disposition by age and by haemophilia severity at inclusion – all patients

	Age at inclusion			Haemophilia severity at inclusion[+]		
	Baseline age < 12 years	**Baseline age ≥ 12 years**	**Total**	**Severe**	**Moderately Severe**	**Total**
Screened			70			70
Included in study	14 (100.0)	55 (100.0)	69 (100.0)	58 (100.0)	10 (100.0)	69 (100.0)
Withdrawals	5 (35.7)	6 (10.9)	11 (15.9)	8 (13.8)	3 (30.0)	11 (15.9)
Protocol violation	1 (7.1)	0 (0.0)	1 (1.4)	0 (0.0)	1 (10.0)	1 (1.4)
Withdrawal by patient	0 (0.0)	6 (10.9)	6 (8.7)	4 (6.9)	2 (20.0)	6 (8.7)
Other	4 (28.6)	0 (0.0)	4 (5.8)	4 (6.9)	0 (0.0)	4 (5.8)
Completed study	9 (64.3)	49 (89.1)	58 (84.1)	50 (86.2)	7 (70.0)	58 (84.1)
Full analysis set	14 (100.0)	54 (98.2)	68 (98.6)	58 (100.0)	9 (90.0)	68 (98.6)
Prophylactic regimen	14 (100.0)	49 (89.1)	63 (91.3)	55 (94.8)	8 (80.0)	63 (91.3)
On-demand regimen	0 (0.0)	5 (9.1)	5 (7.2)	3 (5.2)	1 (10.0)	5 (7.2)
Safety analysis set	14 (100.0)	54 (98.2)	68 (98.6)	58 (100.0)	9 (90.0)	68 (98.6)
Number of visits	40	248	288	248	37	288
Years in study*	12.5	75.2	87.8	76.3	10.4	87.8
Prophylactic regimen	12.5	63.5	76.0	67.3	8.7	76.0
On-demand regimen	0	11.7	11.7	9.0	1.7	11.7
EDs in study*	1825	7142	8967	7932	991	8967
Underwent surgery during study	[redacted]	[redacted]	8 (11.6)	4 (6.9)	3 (30.0)	8 (11.6)
Completed study with <100 ED**	0 (0.0)	8 (14.5)	8 (11.6)	6 (10.3)	1 (10.0)	8 (11.6)

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.

[+] 1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.

The full analysis set and the safety analysis set both consists of all patients exposed to FVIII during study participation.

*The sum for all patients in FAS, across all visits, is presented. ED: Exposure day.

**Principal Investigator has confirmed and signed that although the patients recorded less than 100 EDs, the patients have completed the study.

Cross-reference: modified based on EOT Tables 14.2.1 and 14.2.2

[redacted] [redacted]

Table 10-3 Exposure of turoctocog alfa during the study by age and by haemophilia severity at inclusion – FAS

	Age at inclusion			Haemophilia severity at inclusion[+]		
	Baseline age < 12 years	Baseline age ≥ 12 years	Total	Severe	Moderately Severe	Total
Number of patients	14	54	68	58	9	68
Exposure days per patient*						
N	14	54	68	58	9	68
Mean (SD)	130.4 (88.1)	132.3 (102.4)	131.9 (99.0)	136.8 (102.4)	110.1 (74.9)	131.9 (99.0)
Median	113.0	122.0	120.5	123.5	111.0	120.5
Min; Max	32.0; 337.0	7.0; 766.0	7.0; 766.0	7.0; 766.0	17.0; 245.0	7.0; 766.0
Exposure days for prophylaxis per patient						
N	14	49	63	55	8	63
Mean (SD)	126.7 (88.3)	131.3 (104.7)	130.3 (100.6)	133.7 (104.6)	107.1 (67.7)	130.3 (100.6)
Median	104.0	121.0	121.0	122.0	104.5	121.0
Min; Max	32.0; 337.0	4.0; 766.0	4.0; 766.0	4.0; 766.0	14.0; 240.0	4.0; 766.0
Exposure days for treatment of bleed/surgery per patient						
N	8	39	47	39	7	47
Mean (SD)	6.8 (5.0)	18.3 (23.8)	16.3 (22.1)	15.1 (22.9)	21.6 (19.6)	16.3 (22.1)
Median	5.5	9.0	7.0	7.0	16.0	7.0
Min; Max	2.0; 14.0	1.0; 116.0	1.0; 116.0	1.0; 116.0	1.0; 57.0	1.0; 116.0

N: Number of patients, SD: Standard deviation.

* Includes all prophylaxis, treatment of bleed or surgery exposure days.

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.

[+] 1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.

Cross-reference: modified based on EOT Tables 14.2.33 and 14.2.34

10.1.1 Protocol deviations

Summary of important protocol deviations

Protocol deviations (PDs) were categorised as important/non-important and into different categories according to a set of pre-specified categories (Table 10-4). Important PDs were considered those that could significantly impact the completeness, accuracy and/or reliability of the study data or that could significantly affect the patients' rights, safety or well-being.

This section describes important PDs closed by DBL (17 March 2020). Listings of all important PDs reported with description and action taken are provided in Annex 2, Document 16.2.2.

In total, there were 71 important PDs; 1 at study-level, 1 at country-level, 2 at site-level and 67 at patient-level (Annex 2, Document 16.2.2).

None of the important PDs were considered to have an overall impact on study conduct, patient safety or data interpretation.

Important protocol deviations at study-level

There was 1 important study-level PD in the category 'PD important - other'.

The PD was related to the missing updated flowchart page in the CRF. The CRF was updated to reflect the changes as per protocol amendment no. 4 dated 13 January 2017 (see Section 8) and was distributed to the affiliates on November 2017. However, the distributed CRF did not contain the updated flowchart page. On 10 March 2018, the updated flowchart was distributed to the affiliates.

For further details regarding study-level PD, see Annex 2, Document 16.2.2, Listing 16.2.2.1.

Important protocol deviation at country-level

There was 1 important country-level PD in the category 'PD important - other'.

The PD was related to the delayed submission of the global protocol amendment no. 4 to multicentric ethics committee in Slovakia. The global protocol amendment no. 4 dated 13 January 2017 was submitted to multicentric ethics committee on 10 April 2018, which was approximately 4 months late, and approval was obtained on 24 April 2018.

For further details regarding country-level PD, see Annex 2, Document 16.2.2, Listing 16.2.2.2.

Important protocol deviation at site-level and patient-level

There were 2 important site-level PDs reported in this study. Full description of the site-level PDs is provided in Annex 2, Document 16.2.2, Listings 16.2.2.3 and 16.2.2.5.

Overall, 67 important patient-level PDs were reported; [redacted] (Annex 2, Document 16.2.1, Listings 16.2.1.1). The patient-level PDs by deviation category is presented in Table 10-4 and full description of the patients-level PDs is provided in Annex 2, Document 16.2.2, Listings 16.2.2.4 and 16.2.2.6.

Table 10-4 Summary of important protocol deviations at patient-level

Protocol deviation category	Patient-level PDs
Informed consent	44
Incl./Excl./Rand. Criteria	5
Withdrawal Criteria	1
Assessment Deviations (incl. lab)	5
Other	12

Cross-reference: based on Annex 2, Document 16.2.2

A summary of the important site-level and patient-level PDs by category is provided below:

Informed consent

There were 1 important site-level PD and 44 important patient-level PDs reported in the 'informed consent' category.

The site-level PD was related to missing reconsent of updated informed consent form (ICF) for all patients at the site. The ICF was updated with the extended study duration and new telephone numbers.

[redacted]

The majority of the patient-level PDs were due to procedural issues in informed consent process, missing or delayed re-consent and wrong version of informed consent signed by the patient at screening visit.

All informed consent related PDs were adequately addressed. As a corrective action, site staff was re-trained on informed consent procedure, GCP requirement and respective IEC/IRB (or other appropriate body as required locally) was informed as applicable.

Inclusion/exclusion/randomization criteria

A total of 5 important patient-level PDs were reported in the 'inclusion/exclusion/randomisation criteria' category. Of these, 4 PDs were due to violation of inclusion criterion # 5 (negative FVIII inhibitor test obtained not more than 4 weeks prior to first dosing with turoctocog alfa) and 1 PD was due to violation of exclusion criterion # 5 (previous participation in any clinical trial with turoctocog alfa). All patients were allowed to remain in the study.

Withdrawal criteria

One (1) important patient-level PD was reported in the 'withdrawal criteria' category. The patient withdrew from the study, as the patient started treatment with another product other than turoctocog alfa after enrolment into the study.

Assessment deviation

There were 5 important patient-level PDs reported in the 'assessment deviation' category. The PDs were related to diary not being provided to the patients (2 PDs), diary not being filled by the patient (1 PD) and diary not being returned by the patient (1 PD). In addition, 1 PD was related to [redacted] sample obtained for FVIII inhibitor test.

Other

There was 1 important site-level PD and 12 important patient-level PDs reported in the 'other' category.

The site-level PD was related to the study task performed by site staff who was not delegated to the task.

Of the 12 patient-level PDs, 3 PDs concerned to missing data in the study diary, 2 PDs concenrned privacy statement of genetic data not signed and general practitioner copy not present at the site, and 2 PDs concerned personal data processing form not signed by the patient. Other individual PDs concerned information notice signed after the injection, late reporting of the follow up information of the serious adverse reaction to the sponsor, loss of diary, patient not using study diary and patient signed ICF before agreement being signed with the hospital and physician.

Important protocol deviations closed or identified after database lock

There were no important PDs identified or closed after DBL.

10.2 Descriptive data

10.2.1 Patient demographics

Patient baseline demographics by age and by haemophilia severity at inclusion is presented in Table 10-5.

At baseline, the mean (SD) age for patients <12 years of age group was 7.4 (2.3) years and ≥12 years of age group was 33.6 (15.5) years. The study population consisted of 50 white patients ([redacted]) and 4 Asian patients ([redacted]). The race for 3 patients ([redacted]) was reported as 'other' [redacted]. The race and ethnicity was reported as "not available" for 11 patients ([redacted]) (Table 10-5 and Annex 2, Document 16.2.4, Listing 16.2.4.3).

There were 13 patients from the Netherlands, 11 patients from Germany, 10 patients from Italy, 9 patients from France, 6 patients from Poland, 4 patients from Slovenia, 3 patients from each Slovakia, Greece and Austria, 2 patients from both Hungary and United States of America, and 1 patient from each Switzerland and Czech Republic included in the study (Table 10-5).

At baseline, the mean (SD) height and mean (SD) body weight for patients <12 years of age group was 132.8 (16.0) cm and 31.9 (13.1) kg, respectively. The mean (SD) height and mean (SD) body weight for patients ≥12 years of age group was 175.3 (7.6) cm and 78.0 (15.7) kg, respectively (EOT Table 14.1.3).

Body measurements and vital signs at baseline by age and by haemophilia severity at inclusion are presented in EOT Tables 14.1.3 to 14.1.6. Demographics and baseline characteristics including body measurements are listed in Annex 2, Document 16.2.4, Listing 16.2.4.3.

Table 10-5 Baseline demographics by age and by haemophilia severity at inclusion - FAS

	Age at inclusion			Haemophilia severity at inclusion+		
	Baseline age < 12 years	Baseline age ≥ 12 years	Total	Severe	Moderately Severe	Total
Number of patients	14	54	68	58	9	68
Age at baseline (years)						
N	14	54	68	58	9	68
Mean (SD)	7.4 (2.3)	33.6 (15.5)	28.2 (17.4)	26.2 (15.5)	38.6 (24.8)	28.2 (17.4)
Median	6.5	31.0	26.5	25.0	28.0	26.5
Min; Max	5; 11	12; 76	5; 76	5; 63	11; 76	5; 76
Country, N (%)						
N	14 (100.0)	54 (100.0)	68 (100.0)	58 (100.0)	9 (100.0)	68 (100.0)
Austria	[redacted]		3 (4.4)	[redacted]		3 (4.4)

[redacted]

Czech Republic	[redacted]		1 (1.5)	[redacted]		1 (1.5)
France			9 (13.2)			9 (13.2)
Germany			11 (16.2)			11 (16.2)
Greece			3 (4.4)			3 (4.4)
Hungary			2 (2.9)			2 (2.9)
Italy			10 (14.7)			10 (14.7)
Netherlands			13 (19.1)			13 (19.1)
Poland			6 (8.8)			6 (8.8)
Slovakia			3 (4.4)			3 (4.4)
Slovenia			4 (5.9)			4 (5.9)
Switzerland			1 (1.5)			1 (1.5)
United States of America			2 (2.9)			2 (2.9)
Ethnicity, N (%)						
N	[redacted]		68 (100.0)	[redacted]		68 (100.0)
Hispanic or Latino			2 (2.9)			2 (2.9)
Not Hispanic or Latino			55 (80.9)			55 (80.9)
NA						11 (16.2)
Race, N (%)						
N	14 (100.0)	54 (100.0)	68 (100.0)	58 (100.0)	9 (100.0)	68 (100.0)
Asian	[redacted]					4 (5.9)
White						50 (73.5)
Other						3 (4.4)
Not Available						11 (16.2)
Undergone surgery prior to Study*, N (%)						
N	14 (100.0)	54 (100.0)	68 (100.0)	58 (100.0)	9 (100.0)	68 (100.0)
Yes	6 (42.9)	29 (53.7)	35 (51.5)	29 (50.0)	5 (55.6)	35 (51.5)
No	8 (57.1)	25 (46.3)	33 (48.5)	29 (50.0)	4 (44.4)	33 (48.5)
Years in surgery prior to study*	0.06	1.22	1.28	0.99	0.12	1.28

N: Number of patients, %: Percentage of patients, NA: Not available, SD: Standard deviation

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.

[+] 1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.

* Any surgeries within the last 5 years before the start of the study.

Cross-reference: modified based on EOT Tables 14.1.1 and 14.1.2

10.2.2 Concomitant medication, concomitant illness and medical history at baseline

Concomitant medication at baseline by age and by haemophilia severity at inclusion is presented in EOT Tables 14.1.7 and 14.1.8, respectively. Concomitant medications are listed in Annex 2, Document 16.2.4, Listing 16.2.4.9.

A total of 42 patients reported any concomitant illness at baseline. The most common concomitant illness reported at baseline were haemophilic arthropathy (N=11, 16.2%), hepatitis C (N=11, 16.2%), hypertension (N=9, 13.2%) and arthropathy (N=6, 8.8%). The summary of concomitant illness at baseline by age and by haemophilia severity at inclusion is presented in EOT Tables 14.1.9 and 14.1.10, respectively. Individual patient's concomitant illness/medical history are listed in Annex 2, Document 16.2.4, Listing 16.2.4.10.

** In the interim analysis report, number of concomitant illness were reported; however, in final analysis report, number of patients with concomitant illness have been reported to align with project standards.*

The majority (N=58, 86.6%) of the patients had severe haemophilia (FVIII level <1%), 9 patients (13.4%) had moderately severe haemophilia (FVIII level: 1-2%); apart from this 1 patient had FVIII level >2% at inclusion (see section 10.2.1). Details of haemophilia by age at inclusion is presented in EOT Table 14.1.11 and by haemophilia severity at inclusion is presented in Table 10-6. Details of haemophilia are listed in Annex 2, Document 16.2.4, Listing 16.2.4.4.

Table 10-6 Details of haemophilia by haemophilia severity at inclusion - FAS

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Classification of Haemophilia A Severity, N (%)			
N	58 (100.0)	9 (100.0)	67 (100.0)
Moderately Severe	-	9 (100.0)	9 (13.4)
Severe	58 (100.0)	-	58 (86.6)
FVIII level (%) from medical history, N (%)			
N	58 (100.0)	9 (100.0)	67 (100.0)
<1	58 (100.0)	-	58 (86.6)
<2	-	9 (100.0)	9 (13.4)
Suspicion of inhibitors from medical history*, N (%)			
N	58 (100.0)	9 (100.0)	68 (100.0)
Yes	6 (10.3)	-	6 (8.8)
No	52 (89.7)	9 (100.0)	62 (91.2)
Inhibitor tests taken, N (%)			
N	58 (100.0)	9 (100.0)	68 (100.0)
Yes	57 (98.3)	9 (100.0)	67 (98.5)
No	1 (1.7)	-	1 (1.5)
FVIII recovery tests taken, N (%)			
N	58 (100.0)	9 (100.0)	68 (100.0)
Yes	30 (51.7)	6 (66.7)	36 (52.9)
No	25 (43.1)	3 (33.3)	29 (42.6)
Missing	3 (5.2)	-	3 (4.4)
Most recent recovery test result, (IU/mL)			
N	28	6	34
Mean (SD)	59.0 (46.3)	67.0 (52.2)	60.4 (46.6)
Median	55.1	66.6	55.1
Min ; Max	1.8 ; 154.4	0.7 ; 142.0	0.7 ; 154.4

N: Number of patients, %: Percentage of patients, SD: Standard deviation.
Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
* Including transient inhibitors.

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Cross-reference: EOT Table 14.1.12

A total of 6 patients ([redacted]) reported clinical suspicion of inhibitor based on the medical history. Listing of patients with clinical suspicion of inhibitors is presented in Annex 2, Document 16.2.4, Listing 16.2.4.8. Five (5) of the 6 patients were tested for FVIII inhibitors during the study and 1 patient was not tested (Annex 2, Document 16.2.8, Listing 16.2.8.4).

A total of 41 (60.3%) patients had a family history of haemophilia A. Of these, relatives of 6 patients (8.8%) (all ≥12 years and severe haemophilia) had history of positive inhibitors (EOT Tables 14.1.15 and 14.1.16). Out of 6 patients, 5 were tested for FVIII inhibitors (Annex 2, Document 16.2.8, Listing 16.2.8.4). The family history of haemophilia by age and by haemophilia severity at inclusion is presented in EOT Tables 14.1.15 and 14.1.16, respectively. Details of family history of haemophilia are listed in Annex 2, Document 16.2.4, Listing 16.2.4.5.

[redacted]

Prior to entry into the study, a total of 5 patients (all ≥12 years) were on on-demand regimen: 3 patients with severe haemophilia, 1 patient with moderately severe haemophilia and 1 patient with FVIII level >2% (EOT Tables 14.1.17, 14.1.18 and Annex 2, Document 16.2.4, Listing 16.2.4.7). The mean (SD) number of months that patients had been on on-demand regimen was 33.6 (17.4) months. The mean (SD) number of bleeds within the last 50 EDs or 2 years for patients on on-demand regimen was 22.6 (11.2) bleeds/patient/year (EOT Tables 14.1.17 and 14.1.18).

A total of 63 patients (14 patients <12 years and 49 patients ≥12 years) were on prophylaxis regimen: 55 patients with severe haemophilia and 8 patients with moderately severe haemophilia. The mean (SD) number of months that patients had been on prophylaxis regimen was 23.7 (34.9) months (27.2 (29.9) months for patients <12 years and 22.8 (36.3) months for patients ≥12 years). The mean (SD) number of bleeds within the last 50 EDs or 2 years for patients on prophylaxis regimen was 4.8 (7.5) bleeds/patient/year (3.2 (6.2) bleeds/patient/year for patients <12 years and 5.3 (7.8) bleeds/patient/year for patients ≥12 years) (EOT Tables 14.1.17 and 14.1.18).

The dosage regimen for patients who received prophylaxis regimen was 3 times weekly (N=34, 54.8%), every 2nd day (N=11, 17.7%), once weekly (N=6, 9.7%) and others (N=11, 17.7%) with a mean (SD) dose of 27.7 (12.1) IU/kg (dose range: 0-62 IU/kg) (EOT Tables 14.1.17 and 14.1.18).

A total of 51 patients had a history of switching FVIII products (EOT Tables 14.1.17 and 14.1.18). Details of FVIII product switching are listed in Annex 2, Document 16.2.4, Listing 16.2.4.13.

Haemophilia treatment history for patients who received prophylaxis regimen and on-demand regimen before entry in the study are listed in Annex 2, Document 16.2.4, Listing 16.2.4.6 and 16.2.4.7.

The FVIII genotype by age and by haemophilia severity at inclusion is presented in EOT Tables 14.1.13 and 14.1.14, respectively. Details of the FVIII genotype data are listed in Annex 2, Document 16.2.4, Listing 16.2.4.12.

Of the 68 patients treated with turoctocog alfa, 35 patients underwent surgeries within the last 5 years of the study entry (Table 10-5). Details of surgeries within the last 5 years are listed in Annex 2, Document 16.2.4, Listing 16.2.4.11.

10.3 Outcome data

A total of 69 patients were enrolled into the study, of which 68 patients were exposed to turoctocog alfa, constituting the FAS and SAS.

All safety and efficacy analyses were stratified by age at inclusion (<12 years and ≥12 years) and by haemophilia severity at inclusion (severe and moderately severe).

Of the 68 patients, 14 patients were <12 years of age (13 patients with severe haemophilia and 1 patient with moderately severe haemophilia) and 54 patients were ≥12 years of age (45 patients with severe haemophilia, 8 patients with moderately severe haemophilia and 1 patient with FVIII level >2%) (EOT Table 14.1.11 and Annex 2, Document 16.2.4, Listing 16.2.4.4).

10.4 Main results

10.4.1 Primary endpoint

The primary endpoint was incidence rate of FVIII inhibitors (≥0.6 BU for central laboratory analyses, or above the specific local laboratory reference range) represented as the percentage of patients developing inhibitors.

None of the patients had reported FVIII inhibitor development (≥0.6 BU) during treatment with turoctocog alfa (EOT Tables 14.2.28 and 14.2.29).

Of the 68 exposed patients, 55 patients had at least one inhibitor test post-baseline and all of them reported negative FVIII inhibitor test result (Annex 2, Document 16.2.8, Listing 16.2.8.4). A total of 6 patients completed the study without any inhibitor test taken, and for 7 patients inhibitor test result was reported only at baseline visit (Annex 2, Document 16.2.8, Listing 16.2.8.4); therefore, these 13 patients were not included in the primary analysis.

An additional question, "*clinical suspicion of an inhibitor since last visit*" was introduced in the CRF version 2. The response to this question was reported by 32 patients for at least 1 post-baseline visit and there were no reported clinical suspicion of inhibitor development (Data on file).

Four (4) of the 13 patients not included in the primary analysis reported absence of clinical suspicion of inhibitor development (Data on file).

A total of 4 patients did not have an inhibitor test done within the 4 weeks prior to starting treatment with turoctocog alfa (see Section 10.1.1). Of these, 3 patients had negative inhibitor test result available during the study (these patients were included in the primary analysis) and for 1 patient, inhibitor test result was not reported during the study (this patient was not included in the primary analysis) (Annex 2, Document 16.2.8, Listing 16.2.8.4).

Incidence rate of inhibitor by age at inclusion, by haemophilia severity at inclusion and by treatment regimen is presented in EOT Tables 14.2.28, 14.2.29 and 14.2.30, respectively. The Kaplan-Meier plot of time to inhibitor development by age and by haemophilia severity at inclusion is presented in EOT Figures 14.2.31 and 14.2.32, respectively.

Details of FVIII inhibitors by visit and during surgery are listed in Annex 2, Document 16.2.8, Listing 16.2.8.4 and 16.2.8.5, respectively.

The total number of patients who were tested for FVIII inhibitors at baseline and at last visit by age and by haemophilia severity at inclusion is presented in EOT Tables 14.3.5.5 and 14.3.5.6, respectively. Details of FVIII recovery levels at baseline and at last visits by age and by haemophilia severity at inclusion is presented in EOT Tables 14.3.5.3 and 14.3.5.4, respectively.

10.4.2 Secondary endpoints

The secondary endpoints included both efficacy and safety endpoints and are presented in Section 10.4.2.1 and 10.6.1, respectively.

10.4.2.1 Secondary efficacy endpoints

Details of Bleeds

Forty-six (46) of the 68 patients reported a total of 469 bleeding episodes. Of 46 patients with bleeding episodes, 39 patients had severe haemophilia, 6 patients had moderately severe haemophilia and 1 patient had FVIII level >2% at inclusion (Table 10-7, Annex 2, Document 16.2.6, Listing 16.2.6.1 and Annex 2, Document 16.2.3, Listing 16.2.3.2).

Of the 469 bleeds, 308 (65.7%) were spontaneous, 103 (22.0%) were traumatic, and for 58 (12.4%) bleeds, the cause was unknown (Table 10-7).

The most frequent location of the bleeds was in a joint, which accounted for 69.7% of the bleeds. The majority of the bleeds were mild or moderate (N=387, 82.5%) in severity. Details of bleeding episodes by age and by haemophilia severity at inclusion are presented in Table 10-7.

Table 10-7 Details of bleeding episodes by age and by haemophilia severity at inclusion - FAS

	Age at inclusion N (%)			Haemophilia severity at inclusion+ N (%)		
	Baseline age < 12 years	Baseline age ≥ 12 years	Total	Severe	Moderately Severe	Total
Number of bleeding episodes	32	437	469	412	50	469
Number of patients with bleeds	8	38	46	39	6	46
Cause of bleed						
N	32 (100.0)	437 (100.0)	469 (100.0)	412 (100.0)	50 (100.0)	469 (100.0)
Spontaneous	8 (25.0)	300 (68.6)	308 (65.7)	283 (68.7)	19 (38.0)	308 (65.7)
Traumatic	24 (75.0)	79 (18.1)	103 (22.0)	97 (23.5)	5 (10.0)	103 (22.0)
Unknown	-	58 (13.3)	58 (12.4)	32 (7.8)	26 (52.0)	58 (12.4)
Location of bleed						
N	32 (100.0)	437 (100.0)	469 (100.0)	412 (100.0)	50 (100.0)	469 (100.0)
Joint	18 (56.3)	309 (70.7)	327 (69.7)	294 (71.4)	29 (58.0)	327 (69.7)
Gastrointestinal	-	2 (0.5)	2 (0.4)	2 (0.5)	-	2 (0.4)
Mucosal	-	10 (2.3)	10 (2.1)	10 (2.4)	-	10 (2.1)
Muscular	3 (9.4)	48 (11.0)	51 (10.9)	38 (9.2)	11 (22.0)	51 (10.9)

Subcutaneous	4 (12.5)	21 (4.8)	25 (5.3)	23 (5.6)	2 (4.0)	25 (5.3)
Other	7 (21.9)	43 (9.8)	50 (10.7)	42 (10.2)	7 (14.0)	50 (10.7)
Unknown	-	4 (0.9)	4 (0.9)	3 (0.7)	1 (2.0)	4 (0.9)
Therapy other than haemostatic drug						
N	32 (100.0)	437 (100.0)	469 (100.0)	412 (100.0)	50 (100.0)	469 (100.0)
Compression	1 (3.1)	3 (0.7)	4 (0.9)	3 (0.7)	-	4 (0.9)
Ice	5 (15.6)	35 (8.0)	40 (8.5)	38 (9.2)	2 (4.0)	40 (8.5)
Other	-	12 (2.7)	12 (2.6)	10 (2.4)	2 (4.0)	12 (2.6)
Not Used	-	37 (8.5)	37 (7.9)	37 (9.0)	-	37 (7.9)
None	-	1 (0.2)	1 (0.2)	1 (0.2)	-	1 (0.2)
Unknown	26 (81.3)	349 (79.9)	375 (80.0)	323 (78.4)	46 (92.0)	375 (80.0)
Severity of bleed						
N	32 (100.0)	437 (100.0)	469 (100.0)	412 (100.0)	50 (100.0)	469 (100.0)
Mild/Moderate	27 (84.4)	360 (82.4)	387 (82.5)	335 (81.3)	45 (90.0)	387 (82.5)
Severe	1 (3.1)	12 (2.7)	13 (2.8)	9 (2.2)	4 (8.0)	13 (2.8)
Unknown	4 (12.5)	65 (14.9)	69 (14.7)	68 (16.5)	1 (2.0)	69 (14.7)

N: Number of bleeds, %: Percentage of bleeds, Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.

[+] 1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.

Cross-reference: modified based on EOT Tables 14.2.7 and 14.2.8

Out of the 63 patients who were on prophylaxis regimen, a total of 62 patients had more than 1 ED reported and were included in the calculation of bleeding rate (Table 10-8). Additionally, 1 patient reported 1 bleeding episode during treatment with turoctocog alfa with unknown number of EDs. This patient was excluded from the ABR analyses (Annex 2, Document 16.2.6, Listing 16.2.6.1). There were missing diary periods for some patients and those missing diary periods were not accounted in the ABR analyses.

Of the 62 patients, 40 patients (64.5%) (8 patients <12 years and 32 patients ≥12 years) reported a total of 240 bleeding episodes while 22 patients (35.5%) had no bleeds (Table 10-8).

A total of 228 bleeds were reported in the 5 patients (all ≥12 years) who received on-demand treatment (Table 10-9 and EOT Table 14.2.22).

Estimated annualised bleeding rates

The overall estimated ABR for patients on prophylaxis regimen was 3.65 (95% CI: 2.53; 5.25) bleeds/patient/year (Table 10-8). The estimated ABR on prophylaxis regimen for spontaneous bleeds was 2.39 (95% CI: 1.50; 3.81) bleeds/patient/year and for traumatic bleeds was 1.15 (95% CI: 0.76; 1.73) bleeds/patient/year (EOT Tables 14.2.24 to 14.2.27).

The overall estimated ABR for patients on on-demand regimen was 20.28 (95% CI: 12.09; 34.01) bleeds/patient/year (EOT Tables 14.2.22 and 14.2.23).

The details of ABR for patients on prophylaxis regimen by age and by haemophilia severity at inclusion are presented in Table 10-8. The details of ABR for patients on on-demand regimen by age at inclusion is presented in EOT Table 14.2.22 and by haemophilia severity at inclusion is presented in Table 10-9.

Table 10-8 Annualised bleeding rate by age and by haemophilia severity at inclusion - patients on prophylaxis regimen - FAS

	Age at inclusion			Haemophilia severity at inclusion		
	Baseline age < 12 years	**Baseline age ≥ 12 years**	**Total**	**Severe**	**Moderately Severe**	**Total**
Number of patients	14	49	63	55	8	63
N*	14	48	62	54	8	62
Number of patients with bleeds	8 (57.1)	32 (66.7)	40 (64.5)	35 (64.8)	5 (62.5)	40 (64.5)
Total number of bleeds	32	208	240	217	23	240
Mean number of bleeds per patient	2.29	4.33	3.87	4.02	2.88	3.87
Median number of bleeds per patient	1.50	2.00	2.00	2.00	2.50	2.00
Range of bleeds, min; max	0; 7	0; 40	0; 40	0; 40	0; 8	0; 40
Mean observation period per patient (years)	0.89	1.24	1.17	1.20	0.96	1.17
Observation period per patient, min; max, (years)	0.21; 1.71	0.21; 5.06	0.21; 5.06	0.21; 5.06	0.21; 1.97	0.21; 5.06
Total observation period (years)	12.52	59.73	72.25	64.61	7.64	72.25
Negative binomial analysis						
Annualised bleeding rate	2.75	3.90	3.65	3.67	3.37	3.65
95% CI	(1.35, 5.61)	(2.57, 5.92)	(2.53, 5.25)	(2.47, 5.46)	(1.41, 8.06)	(2.53, 5.25)
Poisson analysis						
Annualised bleeding rate	2.56	3.48	3.32	3.36	3.01	3.32
95% CI	(1.36, 4.82)	(2.29, 5.29)	(2.31, 4.78)	(2.25, 5.00)	(1.43, 6.36)	(2.31, 4.78)

Annualised bleeding rate, summary						
Mean (SD)	2.70 (3.52)	3.96 (5.19)	3.67 (4.87)	3.67 (5.01)	3.69 (4.05)	3.67 (4.87)
Median (IQR)	1.34 (4.02)	2.14 (6.56)	1.97 (6.19)	1.93 (6.19)	2.76 (7.04)	1.97 (6.19)
Min; Max	0.00; 9.99	0.00; 25.50	0.00; 25.50	0.00; 25.50	0.00; 9.91	0.00; 25.50

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.

CI: Confidence interval, SD: Standard deviation, IQR: Interquartile Range

A 95% CI for the annualised bleeding rate is estimated from a negative binomial model, with a sensitivity analysis using a Poisson model allowing for over-dispersion. If the number of patients per subgroup is less than 2, only the Poisson estimate of rate is provided.

* Number of patients with more than one exposure day reported, only these patients are included in the analysis.

Cross-reference: modified based on EOT Tables 14.2.20 and 14.2.21

Table 10-9 Annualised bleeding rate by haemophilia severity at inclusion - patients on on-demand regimen - FAS

	Severe	Moderately Severe	Total
Number of patients	3	1	5
N*	3	1	5
Number of patients with bleeds	3 (100.0)	1 (100.0)	5 (100.0)
Total number of bleeds	194	27	228
Mean bleeds per patient	64.67	27.00	45.60
Median bleeds per patient	56.00	27.00	37.00
Range of bleeds, min ; max	37 ; 101	27 ; 27	7 ; 101
Mean observation period (years)	2.99	1.69	2.34
Observation period, min ; max, (years)	1.28 ; 5.06	1.69 ; 1.69	1.06 ; 5.06
Total observation period (years)	8.97	1.69	11.72
Negative binomial analysis			
Annualised bleeding rate	25.93	NA	20.28
95% CI	(14.67, 45.84)	NA	(12.09, 34.01)
Poisson analysis			
Annualised bleeding rate	21.63	15.96	19.46
95% CI	(9.77, 47.87)	NA	(10.77, 35.15)
Annualised bleeding rate, summary			
Mean (SD)	26.13 (13.92)	15.96 (-)	20.19 (13.18)
Median (IQR)	28.82 (27.45)	15.96 (0.00)	15.96 (17.75)
Min ; Max	11.06 ; 38.51	15.96 ; 15.96	6.62 ; 38.51

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
CI: Confidence interval, SD: Standard deviation, IQR: Interquartile Range
A 95% CI for the annualised bleeding rate is estimated from a negative binomial model, with a sensitivity analysis using a Poisson model allowing for over-dispersion. If the number of patients per subgroup is less than 2, only the Poisson estimate of rate is provided.
* Number of patients with more than one exposure day reported, only these patients are included in the analysis.
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Cross-reference: EOT Table 14.2.23

Haemostatic effect

The haemostatic response after treatment of a bleed with turoctocog alfa was evaluated on a 4-point scale as 'Excellent', 'Good', 'Moderate' or 'None' (see Section 9.9.2.2). The treatment of a bleed was considered as a 'successful' if the haemostatic response rated as 'Excellent' or 'Good'. If the haemostatic response was rated as 'Moderate' or 'None' then the treatment was considered as 'failure'. An additional analysis was conducted considering missing response along with 'Moderate' or 'None' as 'failure'.

Based on the haemostatic responses collected from NN diaries, haemostatic evaluation ratings were available for 361 bleeds in 37 patients.

The overall success rate of turoctocog alfa for the treatment of bleeds was 87.3% (excluding bleeds for which there was no outcome reported). The haemostatic response for 92 (25.5%) bleeds was rated as 'Excellent', 223 (61.8%) bleeds was rated as 'Good' and 37 (10.2%) bleeds was rated as 'Moderate'. For 9 (2.5%) bleeds the response rating was rated as 'None' (Table 10-10).

A more conservative approach (considering an additional 63 bleeds, for which there was no reported/missing outcome, as treatment failures) gave a success rate of 74.3% for treatment of bleeds (EOT Tables 14.2.13 and 14.2.14).

A summary of the haemostatic effect of turoctocog alfa in the treatment of bleeds when excluding bleeds with a missing response in the analysis is presented by age at inclusion in Table 10-10 and by haemophilia severity at inclusion in EOT Table 14.2.12. The haemostatic effect when including bleeds with a missing response in the analysis is presented by age and by haemophilia severity at inclusion in EOT Tables 14.2.13 and 14.2.14, respectively. Listing of bleeding episodes by patient is presented in Annex 2, Document 16.2.6, Listing 16.2.6.1. The haemostatic effect when excluding bleeds with a missing response in the analysis is presented by severity of bleeding episode in EOT Table 14.2.19.

Table 10-10 Haemostatic effect of turoctocog alfa in the treatment of bleeds by age at inclusion - excluding missing responses - FAS

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Number of patients with bleeding episodes*	7	30	37
Number of bleeding episodes	23	338	361
Haemostatic response, N (%)			
N	23 (100.0)	338 (100.0)	361 (100.0)
Excellent	15 (65.2)	77 (22.8)	92 (25.5)
Good	8 (34.8)	215 (63.6)	223 (61.8)
Moderate	-	37 (10.9)	37 (10.2)
None	-	9 (2.7)	9 (2.5)
Success rate, N (%)			
N	23 (100.0)	338 (100.0)	361 (100.0)
Success	23 (100.0)	292 (86.4)	315 (87.3)
Failure	-	46 (13.6)	46 (12.7)

N: Number of bleeds, %: Percentage of bleeds
Success is defined as either Excellent or Good. Failure is defined as either Moderate or None.
* Number of patients with bleeding episodes using NN diary where haemostatic response is collected.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_haemeff.sas/14200070_haemeff_age1.txt

Cross-reference: EOT Table 14.2.11

A total of 8 patients underwent 11 surgeries (Annex 2, Document 16.2.6, Listing 16.2.6.2). The haemostatic response was available for 7 surgeries (4 surgeries in 3 patients with severe haemophilia, 2 surgeries in 2 patients with moderately severe haemophilia and 1 surgery in a patient with FVIII level >2%). Of these 7 surgeries, haemostatic response for 5 surgeries was rated as 'Excellent' and for 2 surgeries the response was rated as 'Good' (Table 10-11). The overall success rate for haemostatic effect of turoctocog alfa during surgical procedures was 100% (EOT Tables 14.2.15 to 14.2.18 and Annex 2, Document 16.2.6, Listing 16.2.6.2).

Table 10-11 Details of major surgeries with Haemostatic response

Patient	Age at baseline	Surgery Indication	Date of surgery	Surgical procedure	Clinical narrative of procedure	Haemostatic response
[redacted]						Excellent
						Excellent
						Good
						Excellent
						Good
						Excellent
						Excellent

* It was confirmed that turoctocog alpha was used during surgery by the physician, but the dose was not reported in the CRF for both surgeries.

**As reported by investigator

Cross-reference: Based on Annex 2, Document 16.2.6, Listing 16.2.6.2 and Annex 2, Document 16.2.4, Listing 16.2.4.3

Number of injections of turoctocog alfa used for treatment of bleeds

Of the 469 reported bleeds, 234 (49.9%) bleeds were stopped with 1 injection of turoctocog alfa, 99 (21.1%) bleeds were stopped with 2 injections and 68 (14.5%) bleeds were stopped with 3 injections. The mean number of injections required from start to stop of a bleed were 2.6 injections/bleed and the median number of injections were 2 injections/bleed (Table 10-12).

The number of injections of turoctocog alfa required to stop bleeds by age at inclusion is presented in Table 10-12 and by haemophilia severity at inclusion is presented in EOT Table 14.2.10.

Table 10-12 Number of Injections of turoctocog alfa per bleeding episode by age at inclusion - FAS

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of Patients	14	54	68
Number of Patients with bleeding episodes, N*(%)	8(57.1)	38(70.4)	46(67.6)
Injections to treat the bleed, from start to stop of the bleed, N(%)			
N	32(100.0)	437(100.0)	469(100.0)
1 injection	12(37.5)	222(50.8)	234(49.9)
2 injections	12(37.5)	87(19.9)	99(21.1)
3 injections	2(6.3)	66(15.1)	68(14.5)
4 injections	1(3.1)	19(4.3)	20(4.3)
5 injections	4(12.5)	9(2.1)	13(2.8)
6 injections	1(3.1)	10(2.3)	11(2.3)
7 injections	-	2(0.5)	2(0.4)
8 injections	-	5(1.1)	5(1.1)
9 injections	-	2(0.5)	2(0.4)
10 injections	-	3(0.7)	3(0.6)
11 injections	-	3(0.7)	3(0.6)
12 injections	-	1(0.2)	1(0.2)
14 injections	-	1(0.2)	1(0.2)
16 injections	-	1(0.2)	1(0.2)
17 injections	-	1(0.2)	1(0.2)
20 injections	-	1(0.2)	1(0.2)
21 injections	-	1(0.2)	1(0.2)
22 injections	-	1(0.2)	1(0.2)
48 injections	-	1(0.2)	1(0.2)
69 injections	-	1(0.2)	1(0.2)
Injection to stop the bleed			
N	32	437	469
Mean (SD)	2.25 (1.48)	2.63 (4.68)	2.60 (4.53)
Median(IQR)	2.00 (1.50)	1.00 (2.00)	2.00 (2.00)
Min ; Max	1.00 ;6.00	1.00 ;69.00	1.00 ;69.00

N*: Number of Patients, N: Number of bleeds, SD: Standard deviation, IQR: Interquartile Range
Number of Infusions to Treat the Bleed is calculated as the number of infusions of turoctucog alfa given per patient and bleed which includes all doses given between start and stop date of the bleed.

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Cross-reference: modified from EOT Table 14.2.9

Consumption of turoctocog alfa

The mean (SD) consumption of turoctocog alfa per patient per month (including all doses given as prophylaxis regimen and for the treatment of bleed or surgery) was 309.0 (191.8) IU/kg/month (N=68, range: 10.8−853.2 IU/kg/month). The mean (SD) consumption of turoctocog alfa for prophylaxis regimen per patient per month was 302.9 (165.1) IU/kg/month. The mean (SD) consumption of turoctocog alfa per bleed was 58.0 (99.0) IU/kg/bleed and consumption for surgery was 145.9 (171.6) IU/kg (Table 10-13).

The mean (SD) average dose of turoctocog alfa for prophylaxis regimen per patient per exposure day was 30.1(11.4) IU/kg/ED. The mean (SD) average dose of turoctocog alfa per bleed per injection was 23.8 (10.4) IU/kg/bleed (Table 10-13).

Summary of consumption of turoctocog alfa by age and by haemophilia severity at inclusion is presented in Table 10-13. Listing of treatment administration by patient is presented in Annex 2, Document 16.2.5, Listing 16.2.5.1 and in peri-surgery is listed in Annex 2, Document 16.2.5, Listing 16.2.5.2.

Table 10-13 Consumption of turoctocog alfa during the study by age and by haemophilia severity at inclusion - FAS

	Age at inclusion			Haemophilia severity at inclusion≠		
	Baseline age < 12 years	Baseline age ≥ 12 years	Total	Severe	Moderately Severe	Total
Number of patients	14	54	68	58	9	68
Total consumption of turoctocog alfa* per patient per month (IU/kg/month)**						
N	14	54	68	58	9	68
Mean (SD)	391.2 (141.3)	287.7 (198.4)	309.0 (191.8)	312.0 (162.9)	316.8 (333.4)	309.0 (191.8)
Median	351.0	277.4	320.3	327.8	155.2	320.3
Min; Max	155.2; 653.5	10.8; 853.2	10.8; 853.2	10.8; 687.7	27.8; 853.2	10.8; 853.2
Consumption of turoctocog alfa for prophylaxis per patient per month+ (IU/kg/month)						
N	14	49	63	55	8	63
Mean (SD)	376.1 (139.8)	282.0 (167.1)	302.9 (165.1)	307.4 (155.8)	271.8 (230.2)	302.9 (165.1)
Median	350.8	283.3	301.2	312.1	167.5	301.2
Min; Max	155.2; 649.6	5.3; 656.0	5.3; 656.0	5.3; 656.0	21.6; 650.5	5.3; 656.0
Consumption of turoctocog alfa per bleed* (IU/kg/bleed)**						
N	32	436	468	411	50	468
Mean (SD)	70.9 (60.5)	57.1 (101.2)	58.0 (99.0)	46.8 (49.5)	147.4 (246.7)	58.0 (99.0)
Median	47.2	31.0	31.3	31.3	26.1	31.3

Min; Max	23.8; 250.0	7.7; 1244.4	7.7; 1244.4	7.7; 525.0	12.5; 1244.4	7.7; 1244.4
Consumption of turoctocog alfa for surgery++ (IU/kg)						
N	0	7	7	3	3	7
Mean (SD)	- (-)	145.9 (171.6)	145.9 (171.6)	224.8 (243.7)	43.9 (39.6)	145.9 (171.6)
Median	-	88.4	88.4	150.0	30.8	88.4
Min; Max	-; -	12.5; 497.1	12.5; 497.1	27.2; 497.1	12.5; 88.4	12.5; 497.1
Average dose of turoctocog alfa for prophylaxis per patient per exposure day+ (IU/kg/ED)						
N	14	49	63	55	8	63
Mean (SD)	33.0 (9.3)	29.2 (11.9)	30.1 (11.4)	30.3 (11.2)	28.5 (13.5)	30.1 (11.4)
Median	29.6	29.7	29.7	29.8	26.3	29.7
Min; Max	22.3; 55.3	9.9; 57.3	9.9; 57.3	9.9; 57.3	10.4; 50.3	9.9; 57.3
Average dose of turoctocog alfa per bleed per injection* (IU/kg/bleed)**						
N	32	436	468	411	50	468
Mean (SD)	31.2 (12.6)	23.3 (10.1)	23.8 (10.4)	23.5 (10.3)	28.8 (8.9)	23.8 (10.4)
Median	27.3	23.8	24.1	23.8	26.1	24.1
Min; Max	15.2; 62.5	5.4; 55.6	5.4; 62.5	6.4; 62.5	12.5; 50.3	5.4; 62.5

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.

≠ 1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.

SD: Standard deviation.

* Consumption includes all doses given for prophylaxis, treatment of bleed or surgery.

** N is number of patients with more than one exposure day reported.

*** N is number of bleeds.

+ N is number of patients on prophylaxis/preventive regimen with more than one exposure day reported

++ N is number of patients with surgeries requiring treatment with turoctocog alfa.

Cross-reference: modified based on EOT Tables 14.2.5 and 14.2.6

10.4.3 Summary of main results

Of the 69 enrolled patients, 68 patients were exposed to turoctocog alfa, constituting the FAS and SAS. A total of 11 patients withdrew from the study. A total of 58 patients (9 patients <12 years and 49 patients ≥12 years) completed the study by having reached 100 EDs or reported by the physician as having completed the study.

Of the 68 exposed patients, 63 patients were on prophylaxis regimen (55 patients with severe haemophilia and 8 patients with moderately severe haemophilia) and 5 patients were on on-demand regimen (3 patients with severe haemophilia, 1 patient with moderately severe haemophilia and 1 patient with FVIII level >2%).

A total of 14 patients were <12 years of age (13 patients with severe haemophilia and 1 patient of moderately severe haemophilia) and 54 patients were ≥12 years of age (45 patients with severe haemophilia, 8 patient with moderately severe haemophilia and 1 patient having FVIII level >2%).

None of the patients had reported FVIII inhibitor development (≥0.6 BU) during treatment with turoctocog alfa.

A total of 469 bleeding episodes were reported in 46 patients. The overall estimated ABR for patients on prophylaxis regimen was 3.65 (95% CI: 2.53; 5.25) bleeds/patient/year and for patients on on-demand regimen was 20.28 (95% CI: 12.09; 34.01) bleeds/patient/year.

For patients on prophylaxis regimen, the estimated ABR was 2.39 bleeds/patient/year for spontaneous bleeds and 1.15 bleeds/patient/year for traumatic bleeds.

Based on the haemostatic responses collected from NN diaries, the haemostatic evaluation ratings were available for 361 bleeds out of 469 bleeds. The overall success rate of turoctocog alfa for the treatment of bleeds was 87.3% (excluding bleeds for which there was no outcome reported). The overall success rate for haemostatic effect of turoctocog alfa during surgical procedures was 100%.

Of the 469 reported bleeds, 234 (49.9%) bleeds were stopped with 1 injection of turoctocog alfa, 99 (21.1%) bleeds were stopped with 2 injections and 68 (14.5%) bleeds were stopped with 3 injections. The mean number of injections required from start to stop of a bleed were 2.6 injections/bleed.

The mean (SD) average dose of turoctocog alfa for prophylaxis regimen per patient per exposure day was 30.1 (11.4) IU/kg/ED. The mean (SD) average dose of turoctocog alfa per bleed per injection was 23.8 (10.4) IU/kg/bleed. The mean (SD) consumption (including all doses given for prophylaxis regimen, treatment of bleed or surgery) of turoctocog alfa per patient per month was 309.0 (191.8) IU/kg/month.

10.5 Other analyses

The section is not applicable for this report.

10.6 Adverse reactions

10.6.1 Secondary safety endpoint

Summary of serious adverse reaction

One (1) serious adverse reaction of angina pectoris was reported.

A [redacted] patient (BMI [redacted]) with severe haemophilia was enrolled into the study [redacted] was treated with a mean dose regimen of [redacted] IU/kg every alternate day. The patient had a medical history of heart disease [redacted] the patient developed angina pectoris [redacted] the patient

[redacted]

continued with turoctocog alfa treatment (Section 14.3.3, EOT Tables 14.3.1.4, 14.3.1.5, 14.3.1.12, 14.3.1.13, 14.3.2.1 and Annex 2, Document 16.2.7, Listing 16.2.7.1).

The serious adverse reaction was moderate in severity and reported to be possibly related to the study drug by the physician (EOT Tables 14.3.1.1 to 14.3.1.3, 14.3.1.7, 14.3.1.10, 14.3.2.1 and Annex 2, Document 16.2.7, Listing 16.2.7.2).

No other adverse reactions were reported during the study (EOT Tables 14.3.1.6, 14.3.1.8, 14.3.1.9 and 14.3.1.11).

10.6.2 Deaths

No adverse reaction leading to death were reported (EOT Table 14.3.2.3).

10.6.3 Other serious adverse reactions

No other serious adverse reaction were reported in the study except from the event of angina pectoris described in Section 10.6.1.

10.6.4 Other significant adverse reactions

There were no AESIs or adverse reactions leading to withdrawal were reported (EOT Tables 14.3.1.14, 14.3.1.15, 14.3.2.2 and Annex 2, Document 16.2.7, Listing 16.2.7.3).

There were no adverse reactions reported in the patient who was not in the safety analysis set (SAS) (Annex 2, Document 16.2.7, Listing 16.2.7.4).

10.6.5 Other observations related to safety

10.6.5.1 Laboratory parameters

The laboratory data was not collected for haematology, biochemistry and viral antibody after protocol amendment no. 4 dated 13 January 2017.

No clinically significant changes in the individual clinical laboratory parameter values were reported as adverse reactions.

The laboratory values collected for FVIII trough levels for baseline and last visit by age and by haemophilia severity at inclusion are summarised in EOT Tables 14.3.5.1 and 14.3.5.2, respectively. The FVIII levels collected by visit are listed in Annex 2, Document 16.2.8, Listing 16.2.8.3. Individual laboratory measurements collected by visit for haematology are listed in Annex 2, Document 16.2.8, Listing 16.2.8.1 and for biochemistry in Annex 2, Document 16.2.8, Listing 16.2.8.2. The viral antibody information collected by patient is listed in Annex 2, Document 16.2.8, Listing 16.2.8.6. Laboratory reference ranges are listed in EOT Table 14.3.4.1 and the limits of quantification are listed in EOT Table 14.3.4.2.

The laboratory results collected outside the reference range are presented in EOT Table 14.3.4.3 (haematology), EOT Table 14.3.4.4 (biochemistry) and EOT Table 14.3.4.6 (FVIII activity).

[redacted]

10.6.5.2 Physical examination

No clinically significant abnormal findings in the individual physical examination were reported as adverse reactions. The individual patients physical examination results by visit is listed in EOT Table 14.3.7.3.

Body measurements (weight (kg) and BMI (kg/m^2)) at baseline and at the last visit are presented in EOT Tables 14.3.6.7 to 14.3.6.10 and individual patients values are listed in EOT Table 14.3.7.2.

10.6.5.3 Vital Signs

Vital signs at baseline and at the last visit are presented in EOT Tables 14.3.6.1 to 14.3.6.6 and individual patients values are listed in EOT Table 14.3.7.1. The vital signs outside the reference range are presented in EOT Table 14.3.4.5. There were no clinically significant changes observed.

10.6.6 Summary of adverse reactions

One (1) serious adverse reaction of angina pectoris was reported. The event was moderate in severity and reported to be possibly related to the study drug by the physician. No other safety concerns were observed in the study.

11 Discussion

The guardian™5 study was a multi-centre, non-interventional PASS designed to provide additional documentation on immunogenicity, safety and efficacy of turoctocog alfa during long-term treatment of patient with severe and moderately severe haemophilia A in routine clinical practice.

A total of 69 patients were enrolled in the study, of which 68 patients were exposed to turoctocog alfa, constituting the FAS and SAS. Of the 68 patients, 14 patients were <12 years of age (13 patients with severe haemophilia and 1 patient of moderately severe haemophilia) and 54 patients were ≥12 years of age (45 patients with severe haemophilia and 8 patients with moderately severe haemophilia and 1 patient with FVIII level >2%).

A total of 58 patients (9 patients <12 years and 49 patients ≥12 years) completed the study by having reached 100 EDs or reported by the physician as having completed the study. The total mean EDs (including all EDs for prophylaxis regimen, treatment of bleed or surgery) per patient was 131.9 (range: 7.0-766.0).

11.1 Key results

Immunogenicity of turoctocog alfa

Development of inhibitor against FVIII is the major concern for haemophilia A treatment. The presence of inhibitor neutralizes the effect of FVIII therapy which may results in increased risk of severe bleeding, development of debilitating haemophilic arthropathy and muscular atrophies leading to reduced quality of life.

None of the patients had reported FVIII inhibitor development (≥0.6 BU) during treatment with turoctocog alfa including 6 patients with clinical suspicion of inhibitor based on the medical history.

Safety of turoctocog alfa

Overall, turoctocog alfa appeared to be well tolerated as no safety concerns have been reported.

One (1) serious adverse reaction of angina pectoris was reported. The event was moderate in severity and reported to be possibly related to the study drug by the physician.

No deaths, AESI and adverse reaction leading to withdrawal were reported. Overall safety findings in this study were consistent with findings from previous turoctocog alfa trials in previously treated patients with congenital FVIII deficiency.

Efficacy of turoctocog alfa

Forty-six (46) of the 68 patients reported a total of 469 bleeding episodes. Most of the bleeds (65.7%) were spontaneous, 22.0% were traumatic and 12.4% were due to reasons unknown. Majority of the bleeding episodes were mild/moderate in severity. The overall estimated ABR for patients on prophylaxis regimen was 3.65 bleeds/patient/year and for patients on on-demand regimen was 20.28 bleeds/patient/year.

The estimated ABR on prophylaxis regimen for spontaneous bleeds was 2.39 bleeds/patient/year and for traumatic bleeds was 1.15 bleeds/patient/year.

Based on the haemostatic responses collected from NN diaries, the haemostatic evaluation ratings were available for 361 bleeds out of 469 bleeds. The haemostatic response was reported as 'Excellent' for 92 (25.5%) bleeds, 'Good' for 223 (61.8%) bleeds, 'Moderate' for 37 (10.2%) bleeds and 'None' for 9 (2.5%) bleeds. The overall success rate for treatment of bleeds with turoctocog alfa was 87.3% (excluding bleeds for which there was no outcome reported). A total of 8 patients underwent 11 surgeries. The haemostatic response was available for 7 surgeries (4 surgeries in 3 patients with severe haemophilia, 2 surgeries in 2 patients with moderately severe haemophilia and 1 surgery in a patient with FVIII level >2%). Of the 7 surgeries, haemostatic response for 5 surgeries was rated as 'Excellent' and for 2 surgeries the response was rated as 'Good'. The overall success rate for haemostatic effect of turoctocog alfa during surgical procedures was 100%.

Of the 469 bleeds, 49.9% of the bleeds were stopped with 1 injection of turoctocog alfa, 21.1% of the bleeds were stopped with 2 injections and 14.5% of the bleeds were stopped with 3 injections. The mean number of injections required from start to stop of a bleed were 2.6 injections/bleed.

The mean (SD) consumption of turoctocog alfa per patient per month (including all doses given as prophylaxis regimen, treatment of bleed or surgery) was 309.0 (191.8) IU/kg/month. The mean (SD) consumption of turoctocog alfa for prophylaxis regimen per patient per month was 302.9 (165.1) IU/kg/month and for surgery was 145.9 (171.6) IU/kg. The mean (SD) consumption of turoctocog alfa per bleed was 58.0 (99.0) IU/kg/bleed (range: 7.7−1244.4 IU/kg/bleed).

Overall success rate for treatment of bleeds reported in present study was comparable to the reported success rate in previously conducted guardian™ clinical programmes.

11.2 Limitations

As this is a non-interventional PASS, there were a number of potential confounding factors that are normally controlled in randomised clinical trials. Refer Section 9.6 for more details on bias. The intention of this non-interventional study was to observe routine treatment of patients. Even though the physicians were encouraged to perform inhibitor test as a routine practice during visits, practices varied between countries. At some sites inhibitor testing was done only when there was a suspicion of inhibitor development and not as a routine practice. This explains the shortage of regular inhibitor tests reported in this study. However, this may be interpreted as an absence of suspicion of inhibitor development.

The study ended when 50 patients were exposed for 100 EDs to study product, therefore some patients were observed for less than 100 EDs.

Some patients used their own diaries instead of NN diary as it was not mandatory to use NN diary. Most of the data were transcribed to the database; however, these diaries did not allow collection of some data points such as haemostatic efficacy.

11.3 Interpretation

The safety and efficacy of turoctocog alfa in treating patients with congenital FVIII deficiency has been consistently demonstrated in this PASS. There were no new safety concerns observed with the

use of turoctocog alfa. No deaths, AESI or adverse reaction leading to withdrawal were reported. No inhibitors against turoctocog alfa were detected during the study period.

Based upon all the available data, benefits of treatment with turoctocog alfa in patients with severe to moderately severe haemophilia A are considered to significantly outweigh the risks.

11.4 Generalisability

The study population included patients who would benefit from turoctocog alfa treatment, based on the indication. The results of this study can be applied only to patients with congenital FVIII deficiency. The very few inclusion and exclusion criteria would reduce the selection bias. As multicentre and multinational population was selected, the generalisability of the study has been evaluated as high.

12 Other information

This section is not applicable for this report.

13 Conclusion

The results from this non-interventional PASS demonstrated that turoctocog alfa treatment in severe and moderately severe haemophilia patients was effective and well tolerated. No FVIII inhibitors were detected and no clinically significant safety issues were identified, indicating that turoctocog alfa is safe.

The study aimed to include at least 10 patients of <12 years old at the time of enrolment. A total 14 patients from <12 years of age and 54 patients from ≥12 years of age were exposed to turoctocog alfa in the study. No specific safety or efficacy related findings for patients from <12 years age group were observed.

In conclusion, based on the clinically identified and proven benefits of turoctocog alfa therapy seen in this study and risk associated with turoctocog alfa therapy, Novo Nordisk A/S evaluates that the benefit-risk profile of turoctocog alfa remains favourable and unchanged with the results of this PASS.

14 Tables, figures and graphs referred to but not included in the text

14.1 Demographic data

14.1.1 Baseline demographics by age at inclusion - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Age at baseline (years)			
N	14	54	68
Mean (SD)	7.4 (2.3)	33.6 (15.5)	28.2 (17.4)
Median	6.5	31.0	26.5
Min ; Max	5 ; 11	12 ; 76	5 ; 76
Country, N (%)			
N	14 (100.0)	54 (100.0)	68 (100.0)
Austria	[redacted]	[redacted]	3 (4.4)
Czech Republic	[redacted]	[redacted]	1 (1.5)
France	[redacted]	[redacted]	9 (13.2)
Germany	[redacted]	[redacted]	11 (16.2)
Greece	[redacted]	[redacted]	3 (4.4)
Hungary	[redacted]	[redacted]	2 (2.9)
Italy	[redacted]	[redacted]	10 (14.7)
Netherlands	[redacted]	[redacted]	13 (19.1)
Poland	[redacted]	[redacted]	6 (8.8)
Slovakia	[redacted]	[redacted]	3 (4.4)
Slovenia	[redacted]	[redacted]	4 (5.9)
Switzerland	[redacted]	[redacted]	1 (1.5)
United States of America	[redacted]	[redacted]	2 (2.9)
Ethnicity, N (%)			
N	14 (100.0)	54 (100.0)	68 (100.0)
Hispanic or Latino	[redacted]	[redacted]	2 (2.9)
Not Hispanic or Latino	[redacted]	[redacted]	55 (80.9)
NA	[redacted]	[redacted]	11 (16.2)
Race, N (%)			
N	14 (100.0)	54 (100.0)	68 (100.0)
Asian	[redacted]	[redacted]	4 (5.9)
White	[redacted]	[redacted]	50 (73.5)
Other	[redacted]	[redacted]	3 (4.4)
NA	[redacted]	[redacted]	11 (16.2)
Undergone surgery prior to Study*, N (%)			
N	14 (100.0)	54 (100.0)	68 (100.0)
Yes	6 (42.9)	29 (53.7)	35 (51.5)
No	8 (57.1)	25 (46.3)	33 (48.5)
Years in surgery prior to study*	0.06	1.22	1.28

N: Number of patients, %: Percentage of patients
NA: Not available, SD: Standard deviation
* Any surgeries within the last 5 years before the start of the study.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_demo.sas/14100010_demoage.txt

[redacted]

14.1.2 Baseline demographics by haemophilia severity at inclusion - full analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Age at baseline (years)			
N	58	9	68
Mean (SD)	26.2 (15.5)	38.6 (24.8)	28.2 (17.4)
Median	25.0	28.0	26.5
Min ; Max	5 ; 63	11 ; 76	5 ; 76
Country, N (%)			
N	58 (100.0)	9 (100.0)	68 (100.0)
Austria	[redacted]	[redacted]	3 (4.4)
Czech Republic	[redacted]	[redacted]	1 (1.5)
France	[redacted]	[redacted]	9 (13.2)
Germany	[redacted]	[redacted]	11 (16.2)
Greece	[redacted]	[redacted]	3 (4.4)
Hungary	[redacted]	[redacted]	2 (2.9)
Italy	[redacted]	[redacted]	10 (14.7)
Netherlands	[redacted]	[redacted]	13 (19.1)
Poland	[redacted]	[redacted]	6 (8.8)
Slovakia	[redacted]	[redacted]	3 (4.4)
Slovenia	[redacted]	[redacted]	4 (5.9)
Switzerland	[redacted]	[redacted]	1 (1.5)
United States of America	[redacted]	[redacted]	2 (2.9)
Ethnicity, N (%)			
N	58 (100.0)	9 (100.0)	68 (100.0)
Hispanic or Latino	[redacted]	[redacted]	2 (2.9)
Not Hispanic or Latino	[redacted]	[redacted]	55 (80.9)
NA	[redacted]	[redacted]	11 (16.2)
Race, N (%)			
N	58 (100.0)	9 (100.0)	68 (100.0)
Asian	[redacted]	[redacted]	4 (5.9)
White	[redacted]	[redacted]	50 (73.5)
Other	[redacted]	[redacted]	3 (4.4)
NA	[redacted]	[redacted]	11 (16.2)
Undergone surgery prior to Study*, N (%)			
N	58 (100.0)	9 (100.0)	68 (100.0)
Yes	29 (50.0)	5 (55.6)	35 (51.5)
No	29 (50.0)	4 (44.4)	33 (48.5)
Years in surgery prior to study*	0.99	0.12	1.28

N: Number of patients, %: Percentage of patients
NA: Not available, SD: Standard deviation
Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
* Any surgeries within the last 5 years before the start of the study.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_demo.sas/14100020_demofviii.txt

14.1.3 Body measurements at baseline by age at inclusion - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Height (cm)			
N	14	50	64
Mean (SD)	132.8 (16.0)	175.3 (7.6)	166.0 (20.3)
Median	126.0	175.0	174.0
Min ; Max	115.0 ; 162.0	140.0 ; 187.0	115.0 ; 187.0
Body weight (kg)			
N	14	51	65
Mean (SD)	31.9 (13.1)	78.0 (15.7)	68.1 (24.4)
Median	28.6	80.0	72.0
Min ; Max	20.0 ; 63.0	37.6 ; 116.0	20.0 ; 116.0
BMI (kg/m^2)			
N	14	50	64
Mean (SD)	17.4 (3.5)	25.4 (4.7)	23.6 (5.6)
Median	16.2	24.9	23.8
Min ; Max	13.4 ; 27.3	16.8 ; 38.9	13.4 ; 38.9

N: Number of patients, %: Percentage of patients.
BMI: body mass index, SD: Standard deviation.
The baseline value for height and weight is the measurement at screening visit 1.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_body.sas/14100030_bodyage.txt

14.1.4 Body measurements at baseline by haemophilia severity at inclusion - full analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Height (cm)			
N	56	7	64
Mean (SD)	165.4 (21.3)	169.0 (10.6)	166.0 (20.3)
Median	174.0	171.0	174.0
Min ; Max	115.0 ; 187.0	155.0 ; 185.0	115.0 ; 187.0
Body weight (kg)			
N	56	8	65
Mean (SD)	66.8 (24.3)	74.2 (25.3)	68.1 (24.4)
Median	72.0	71.0	72.0
Min ; Max	20.0 ; 116.0	43.3 ; 115.0	20.0 ; 116.0
BMI (kg/m^2)			
N	56	7	64
Mean (SD)	23.2 (5.3)	25.9 (7.5)	23.6 (5.6)
Median	23.2	26.3	23.8
Min ; Max	13.4 ; 38.8	16.8 ; 38.9	13.4 ; 38.9

N: Number of patients, %: Percentage of patients.
BMI: body mass index, SD: Standard deviation.
Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column
to represent the full analysis set.
The baseline value for height and weight is the measurement at screening visit 1.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_body.sas/14100040_bodyfviii.txt

14.1.5 Vital signs at baseline by age at inclusion - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Systolic blood pressure (mmHg)			
N	12	34	46
Mean (SD)	99.4 (12.0)	131.4 (11.7)	123.0 (18.4)
Median	96.5	130.0	126.5
Min ; Max	85.0 ; 125.0	110.0 ; 170.0	85.0 ; 170.0
Diastolic blood pressure (mmHg)			
N	12	34	46
Mean (SD)	66.4 (6.0)	77.9 (12.4)	74.9 (12.1)
Median	65.0	79.5	75.0
Min ; Max	55.0 ; 75.0	43.0 ; 120.0	43.0 ; 120.0
Pulse (beats/min)			
N	12	31	43
Mean (SD)	81.8 (12.2)	72.0 (9.7)	74.8 (11.2)
Median	83.5	72.0	74.0
Min ; Max	60.0 ; 96.0	48.0 ; 90.0	48.0 ; 96.0

N: Number of patients, %: Percentage of patients, SD: Standard deviation
The baseline value for vital signs is the measurement at screening visit 1.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_vs.sas/14100050_vsage.txt

14.1.6 Vital signs at baseline by haemophilia severity at inclusion - full analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Systolic blood pressure (mmHg)			
N	39	7	46
Mean (SD)	122.0 (18.4)	128.7 (18.4)	123.0 (18.4)
Median	125.0	133.0	126.5
Min ; Max	85.0 ; 170.0	96.0 ; 150.0	85.0 ; 170.0
Diastolic blood pressure (mmHg)			
N	39	7	46
Mean (SD)	74.4 (11.2)	77.6 (17.3)	74.9 (12.1)
Median	74.0	80.0	75.0
Min ; Max	55.0 ; 120.0	43.0 ; 100.0	43.0 ; 120.0
Pulse (beats/min)			
N	37	6	43
Mean (SD)	75.0 (10.7)	73.2 (15.1)	74.8 (11.2)
Median	74.0	74.5	74.0
Min ; Max	48.0 ; 96.0	52.0 ; 90.0	48.0 ; 96.0

N: Number of patients, %: Percentage of patients, SD: Standard deviation
Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column
to represent the full analysis set.
The baseline value for vital signs is the measurement at screening visit 1.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_vs.sas/14100060_vsfviii.txt

14.1.7 Concomitant medication at baseline by age at inclusion - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Any medication	3 (21.4)	24 (44.4)	27 (39.7)
Adalimumab	-	1 (1.9)	1 (1.5)
Alfuzosin hydrochloride	-	1 (1.9)	1 (1.5)
Alprazolam	-	1 (1.9)	1 (1.5)
Aminocaproic acid	1 (7.1)	1 (1.9)	2 (2.9)
Azelaic acid	-	1 (1.9)	1 (1.5)
Betaxolol hydrochloride	-	1 (1.9)	1 (1.5)
Bisoprolol fumarate	-	1 (1.9)	1 (1.5)
Carvedilol	-	1 (1.9)	1 (1.5)
Cefazolin	-	1 (1.9)	1 (1.5)
Celecoxib	-	1 (1.9)	1 (1.5)
Chondroitin sulfate sodium;salicylate sodium	-	1 (1.9)	1 (1.5)
Cobicistat;elvitegravir;emtricitabine;tenofovir disoproxil fumarate	-	1 (1.9)	1 (1.5)
Colecalciferol	-	2 (3.7)	2 (2.9)
Darunavir ethanolate	-	1 (1.9)	1 (1.5)
Dexamethasone	-	1 (1.9)	1 (1.5)
Diclofenac	-	1 (1.9)	1 (1.5)
Diclofenac sodium	-	1 (1.9)	1 (1.5)
Emtricitabine;tenofovir disoproxil fumarate	-	1 (1.9)	1 (1.5)
Escitalopram	-	1 (1.9)	1 (1.5)
Etoricoxib	-	4 (7.4)	4 (5.9)
Fenofibrate	-	1 (1.9)	1 (1.5)
Folic acid	-	1 (1.9)	1 (1.5)
Hydrochlorothiazide	-	1 (1.9)	1 (1.5)
Hydrochlorothiazide;olmesartan medoxomil	-	1 (1.9)	1 (1.5)
Ibuprofen	-	1 (1.9)	1 (1.5)
Insulin aspart	-	1 (1.9)	1 (1.5)
Insulin glargine	-	1 (1.9)	1 (1.5)
Ledipasvir;sofosbuvir	-	1 (1.9)	1 (1.5)
Metamizole	-	1 (1.9)	1 (1.5)
Methotrexate	-	1 (1.9)	1 (1.5)
Metoclopramide	-	1 (1.9)	1 (1.5)
Moroctocog alfa	-	1 (1.9)	1 (1.5)
Oxycodone hydrochloride	-	3 (5.6)	3 (4.4)
Pantoprazole sodium sesquihydrate	-	3 (5.6)	3 (4.4)
Paracetamol	-	3 (5.6)	3 (4.4)
Paracetamol;tramadol hydrochloride	-	2 (3.7)	2 (2.9)
Peginterferon alfa-2a	-	1 (1.9)	1 (1.5)
Perindopril	-	1 (1.9)	1 (1.5)
Perindopril erbumine	-	1 (1.9)	1 (1.5)
Prednisolone	-	1 (1.9)	1 (1.5)
Ramipril	-	1 (1.9)	1 (1.5)
Ritonavir	-	1 (1.9)	1 (1.5)
Salbutamol	1 (7.1)	-	1 (1.5)
Simvastatin	-	1 (1.9)	1 (1.5)
Tadalafil	-	1 (1.9)	1 (1.5)
Telmisartan	-	1 (1.9)	1 (1.5)
Tramadol	-	1 (1.9)	1 (1.5)
Tranexamic acid	1 (7.1)	1 (1.9)	2 (2.9)

N: Number of patients, %: Percentage of patients.
Generic drug name is reported.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_cmed.sas/14100070_conmedage.txt

14.1.8 Concomitant medication at baseline by haemophilia severity at inclusion - full analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Any medication	20 (34.5)	6 (66.7)	27 (39.7)
Adalimumab	-	1 (11.1)	1 (1.5)
Alfuzosin hydrochloride	-	1 (11.1)	1 (1.5)
Alprazolam	1 (1.7)	-	1 (1.5)
Aminocaproic acid	2 (3.4)	-	2 (2.9)
Azelaic acid	-	1 (11.1)	1 (1.5)
Betaxolol hydrochloride	1 (1.7)	-	1 (1.5)
Bisoprolol fumarate	1 (1.7)	-	1 (1.5)
Carvedilol	-	1 (11.1)	1 (1.5)
Cefazolin	1 (1.7)	-	1 (1.5)
Celecoxib	1 (1.7)	-	1 (1.5)
Chondroitin sulfate sodium;salicylate sodium	1 (1.7)	-	1 (1.5)
Cobicistat;elvitegravir;emtricitabine;tenofovir disoproxil fumarate	1 (1.7)	-	1 (1.5)
Colecalciferol	1 (1.7)	1 (11.1)	2 (2.9)
Darunavir ethanolate	1 (1.7)	-	1 (1.5)
Dexamethasone	-	1 (11.1)	1 (1.5)
Diclofenac	-	1 (11.1)	1 (1.5)
Diclofenac sodium	1 (1.7)	-	1 (1.5)
Emtricitabine;tenofovir disoproxil fumarate	1 (1.7)	-	1 (1.5)
Escitalopram	1 (1.7)	-	1 (1.5)
Etoricoxib	2 (3.4)	2 (22.2)	4 (5.9)
Fenofibrate	-	-	1 (1.5)
Folic acid	-	1 (11.1)	1 (1.5)
Hydrochlorothiazide	-	1 (11.1)	1 (1.5)
Hydrochlorothiazide;olmesartan medoxomil	1 (1.7)	-	1 (1.5)
Ibuprofen	1 (1.7)	-	1 (1.5)
Insulin aspart	1 (1.7)	-	1 (1.5)
Insulin glargine	1 (1.7)	-	1 (1.5)
Ledipasvir;sofosbuvir	1 (1.7)	-	1 (1.5)
Metamizole	-	1 (11.1)	1 (1.5)
Methotrexate	-	1 (11.1)	1 (1.5)
Metoclopramide	1 (1.7)	-	1 (1.5)
Moroctocog alfa	1 (1.7)	-	1 (1.5)
Oxycodone hydrochloride	2 (3.4)	1 (11.1)	3 (4.4)
Pantoprazole sodium sesquihydrate	3 (5.2)	-	3 (4.4)
Paracetamol	3 (5.2)	-	3 (4.4)
Paracetamol;tramadol hydrochloride	2 (3.4)	-	2 (2.9)
Peginterferon alfa-2a	1 (1.7)	-	1 (1.5)
Perindopril	-	-	1 (1.5)
Perindopril erbumine	1 (1.7)	-	1 (1.5)
Prednisolone	1 (1.7)	-	1 (1.5)
Ramipril	1 (1.7)	-	1 (1.5)
Ritonavir	1 (1.7)	-	1 (1.5)
Salbutamol	1 (1.7)	-	1 (1.5)
Simvastatin	-	-	1 (1.5)
Tadalafil	-	1 (11.1)	1 (1.5)
Telmisartan	1 (1.7)	-	1 (1.5)
Tramadol	-	1 (11.1)	1 (1.5)
Tranexamic acid	2 (3.4)	-	2 (2.9)

N: Number of patients, %: Percentage of patients.
Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
Generic drug name is reported.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_cmed.sas/14100080_conmedfviii.txt

14.1.9 Concomitant illness at baseline by age at inclusion - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Any illness	2 (14.3)	40 (74.1)	42 (61.8)
Abdominal hernia	-	1 (1.9)	1 (1.5)
Acne	-	1 (1.9)	1 (1.5)
Appendicectomy	-	1 (1.9)	1 (1.5)
Arthrodesis	-	1 (1.9)	1 (1.5)
Arthropathy	-	6 (11.1)	6 (8.8)
Asthma	-	1 (1.9)	1 (1.5)
Atrial septal defect	-	1 (1.9)	1 (1.5)
[redacted]	-	1 (1.9)	1 (1.5)
Bronchitis chronic	1 (7.1)	-	1 (1.5)
Burnout syndrome	-	1 (1.9)	1 (1.5)
Cataract operation	-	1 (1.9)	1 (1.5)
Cerebral haemorrhage	-	1 (1.9)	1 (1.5)
Cerebrovascular accident	-	1 (1.9)	1 (1.5)
Cholecystectomy	-	1 (1.9)	1 (1.5)
[redacted] hepatitis [redacted]	-	4 (7.4)	4 (5.9)
Dermatitis allergic	-	1 (1.9)	1 (1.5)
Dermatitis contact	-	1 (1.9)	1 (1.5)
Drug hypersensitivity	-	1 (1.9)	1 (1.5)
Dyslipidaemia	-	1 (1.9)	1 (1.5)
Enteritis	-	1 (1.9)	1 (1.5)
Factor VIII deficiency	1 (7.1)	1 (1.9)	2 (2.9)
[redacted]	-	2 (3.7)	2 (2.9)
Haemarthrosis	-	2 (3.7)	2 (2.9)
Haematuria	-	1 (1.9)	1 (1.5)
Haemophilic arthropathy	-	11 (20.4)	11 (16.2)
Haemorrhage intracranial	-	1 (1.9)	1 (1.5)
Haemorrhoids	-	2 (3.7)	2 (2.9)
Hepatic [redacted]	-	1 (1.9)	1 (1.5)
Hepatic [redacted]	-	1 (1.9)	1 (1.5)
Hepatitis [redacted]	-	11 (20.4)	11 (16.2)
Hydrocele	-	1 (1.9)	1 (1.5)
[redacted]	-	1 (1.9)	1 (1.5)
Hypertension	-	9 (16.7)	9 (13.2)
Intervertebral disc protrusion	-	1 (1.9)	1 (1.5)
Knee arthroplasty	-	1 (1.9)	1 (1.5)
Large intestine anastomosis	-	1 (1.9)	1 (1.5)
Ligament rupture	-	1 (1.9)	1 (1.5)
Limb asymmetry	-	1 (1.9)	1 (1.5)
Lower urinary tract symptoms	-	1 (1.9)	1 (1.5)
Medical device removal	-	1 (1.9)	1 (1.5)
Melaena	-	2 (3.7)	2 (2.9)
Obesity	-	1 (1.9)	1 (1.5)
Oesophageal varices haemorrhage	-	1 (1.9)	1 (1.5)
Osteoarthritis	-	4 (7.4)	4 (5.9)
Pain	-	1 (1.9)	1 (1.5)
Paraplegia	-	1 (1.9)	1 (1.5)
Peptic ulcer haemorrhage	-	1 (1.9)	1 (1.5)
[redacted]	-	1 (1.9)	1 (1.5)
Psoriasis	-	1 (1.9)	1 (1.5)
Psoriatic arthropathy	-	1 (1.9)	1 (1.5)
Retinal detachment	-	1 (1.9)	1 (1.5)
Sarcoidosis	-	2 (3.7)	2 (2.9)
Seasonal allergy	-	1 (1.9)	1 (1.5)
Spinal deformity	-	1 (1.9)	1 (1.5)
Synovitis	-	3 (5.6)	3 (4.4)

N: Number of patients, %: Percentage of patients.
Preferred term, MedDRA (v22.1) coding dictionary applied.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_cill.sas/14100090_conillage.txt

Concomitant illness at baseline by age at inclusion - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Talipes	-	1 (1.9)	1 (1.5)
[redacted]	-	1 (1.9)	1 (1.5)
	-	1 (1.9)	1 (1.5)
Type 1 diabetes mellitus	-	1 (1.9)	1 (1.5)
Vitamin D deficiency	-	1 (1.9)	1 (1.5)
Winged scapula	-	1 (1.9)	1 (1.5)

N: Number of patients, %: Percentage of patients.
Preferred term, MedDRA (v22.1) coding dictionary applied.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_cill.sas/14100090_conillage.txt

14.1.10 Concomitant illness at baseline by haemophilia severity at inclusion - full analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Any illness	34 (58.6)	7 (77.8)	42 (61.8)
Abdominal hernia	-	1 (11.1)	1 (1.5)
Acne	-	1 (11.1)	1 (1.5)
Appendicectomy	-	1 (11.1)	1 (1.5)
Arthrodesis	-	1 (11.1)	1 (1.5)
Arthropathy	4 (6.9)	2 (22.2)	6 (8.8)
Asthma	1 (1.7)	-	1 (1.5)
Atrial septal defect	1 (1.7)	-	1 (1.5)
[redacted]	1 (1.7)	-	1 (1.5)
Bronchitis chronic	1 (1.7)	-	1 (1.5)
Burnout syndrome	-	1 (11.1)	1 (1.5)
Cataract operation	-	1 (11.1)	1 (1.5)
Cerebral haemorrhage	1 (1.7)	-	1 (1.5)
Cerebrovascular accident	1 (1.7)	-	1 (1.5)
Cholecystectomy	-	1 (11.1)	1 (1.5)
[redacted] hepatitis [redacted]	2 (3.4)	2 (22.2)	4 (5.9)
Dermatitis allergic	1 (1.7)	-	1 (1.5)
Dermatitis contact	1 (1.7)	-	1 (1.5)
Drug hypersensitivity	-	1 (11.1)	1 (1.5)
Dyslipidaemia	-	-	1 (1.5)
Enteritis	1 (1.7)	-	1 (1.5)
Factor VIII deficiency	2 (3.4)	-	2 (2.9)
[redacted]	2 (3.4)	-	2 (2.9)
Haemarthrosis	2 (3.4)	-	2 (2.9)
Haematuria	-	1 (11.1)	1 (1.5)
Haemophilic arthropathy	10 (17.2)	1 (11.1)	11 (16.2)
Haemorrhage intracranial	1 (1.7)	-	1 (1.5)
Haemorrhoids	2 (3.4)	-	2 (2.9)
Hepatic [redacted]	-	1 (11.1)	1 (1.5)
Hepatic [redacted]	1 (1.7)	-	1 (1.5)
Hepatitis [redacted]	11 (19.0)	-	11 (16.2)
Hydrocele	1 (1.7)	-	1 (1.5)
[redacted]	1 (1.7)	-	1 (1.5)
Hypertension	6 (10.3)	2 (22.2)	9 (13.2)
Intervertebral disc protrusion	1 (1.7)	-	1 (1.5)
Knee arthroplasty	-	1 (11.1)	1 (1.5)
Large intestine anastomosis	1 (1.7)	-	1 (1.5)
Ligament rupture	1 (1.7)	-	1 (1.5)
Limb asymmetry	1 (1.7)	-	1 (1.5)
Lower urinary tract symptoms	-	1 (11.1)	1 (1.5)
Medical device removal	1 (1.7)	-	1 (1.5)
Melaena	-	2 (22.2)	2 (2.9)
Obesity	-	1 (11.1)	1 (1.5)
Oesophageal varices haemorrhage	-	1 (11.1)	1 (1.5)
Osteoarthritis	1 (1.7)	3 (33.3)	4 (5.9)
Pain	1 (1.7)	-	1 (1.5)
Paraplegia	1 (1.7)	-	1 (1.5)
Peptic ulcer haemorrhage	1 (1.7)	-	1 (1.5)
[redacted]	-	1 (11.1)	1 (1.5)
Psoriasis	-	1 (11.1)	1 (1.5)
Psoriatic arthropathy	-	1 (11.1)	1 (1.5)
Retinal detachment	1 (1.7)	-	1 (1.5)
Sarcoidosis	2 (3.4)	-	2 (2.9)
Seasonal allergy	1 (1.7)	-	1 (1.5)

N: Number of patients, %: Percentage of patients.
Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column
to represent the full analysis set.
Preferred term, MedDRA (v22.1) coding dictionary applied.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_cill.sas/14100100_conillfviii.txt

Concomitant illness at baseline by haemophilia severity at inclusion - full analysis set

	Severe	Moderately Severe	Total
Spinal deformity	1 (1.7)	-	1 (1.5)
Synovitis	3 (5.2)	-	3 (4.4)
Talipes	-	1 (11.1)	1 (1.5)
[redacted]	1 (1.7)	-	1 (1.5)
	-	1 (11.1)	1 (1.5)
Type 1 diabetes mellitus	1 (1.7)	-	1 (1.5)
Vitamin D deficiency	-	1 (11.1)	1 (1.5)
Winged scapula	1 (1.7)	-	1 (1.5)

N: Number of patients, %: Percentage of patients.
Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
Preferred term, MedDRA (v22.1) coding dictionary applied.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_cill.sas/14100100_conillfviii.txt

14.1.11 Details of haemophilia by age at inclusion - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Classification of Haemophilia A Severity, N (%)			
N	14 (100.0)	53 (100.0)	67 (100.0)
Moderately Severe	1 (7.1)	8 (15.1)	9 (13.4)
Severe	13 (92.9)	45 (84.9)	58 (86.6)
FVIII level (%) from medical history, N (%)			
N	14 (100.0)	53 (100.0)	67 (100.0)
<1	13 (92.9)	45 (84.9)	58 (86.6)
<2	1 (7.1)	8 (15.1)	9 (13.4)
Suspicion of inhibitors from medical history*, N (%)			
N	14 (100.0)	54 (100.0)	68 (100.0)
Yes	1 (7.1)	5 (9.3)	6 (8.8)
No	13 (92.9)	49 (90.7)	62 (91.2)
Inhibitor tests taken, N (%)			
N	14 (100.0)	54 (100.0)	68 (100.0)
Yes	13 (92.9)	54 (100.0)	67 (98.5)
No	1 (7.1)	-	1 (1.5)
FVIII recovery tests taken, N (%)			
N	14 (100.0)	54 (100.0)	68 (100.0)
Yes	3 (21.4)	33 (61.1)	36 (52.9)
No	11 (78.6)	18 (33.3)	29 (42.6)
Missing	-	3 (5.6)	3 (4.4)
Most recent recovery test result, (IU/mL)			
N	3	31	34
Mean (SD)	46.3 (38.9)	61.8 (47.6)	60.4 (46.6)
Median	63.0	51.6	55.1
Min ; Max	1.8 ; 74.0	0.7 ; 154.4	0.7 ; 154.4

N: Number of patients, %: Percentage of patients, SD: Standard deviation.
* Including transient inhibitors.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_haem.sas/14100110_haemage.txt

[redacted] [redacted]

14.1.12 Details of haemophilia by haemophilia severity at inclusion - full analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Classification of Haemophilia A Severity, N (%)			
N	58 (100.0)	9 (100.0)	67 (100.0)
Moderately Severe	-	9 (100.0)	9 (13.4)
Severe	58 (100.0)	-	58 (86.6)
FVIII level (%) from medical history, N (%)			
N	58 (100.0)	9 (100.0)	67 (100.0)
<1	58 (100.0)	-	58 (86.6)
<2	-	9 (100.0)	9 (13.4)
Suspicion of inhibitors from medical history*, N (%)			
N	58 (100.0)	9 (100.0)	68 (100.0)
Yes	6 (10.3)	-	6 (8.8)
No	52 (89.7)	9 (100.0)	62 (91.2)
Inhibitor tests taken, N (%)			
N	58 (100.0)	9 (100.0)	68 (100.0)
Yes	57 (98.3)	9 (100.0)	67 (98.5)
No	1 (1.7)	-	1 (1.5)
FVIII recovery tests taken, N (%)			
N	58 (100.0)	9 (100.0)	68 (100.0)
Yes	30 (51.7)	6 (66.7)	36 (52.9)
No	25 (43.1)	3 (33.3)	29 (42.6)
Missing	3 (5.2)	-	3 (4.4)
Most recent recovery test result, (IU/mL)			
N	28	6	34
Mean (SD)	59.0 (46.3)	67.0 (52.2)	60.4 (46.6)
Median	55.1	66.6	55.1
Min ; Max	1.8 ; 154.4	0.7 ; 142.0	0.7 ; 154.4

N: Number of patients, %: Percentage of patients, SD: Standard deviation.
Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
* Including transient inhibitors.

nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_haem.sas/14100120_haemfviii.txt

14.1.13 FVIII genotype by age at inclusion - full analysis set

Mutation	Submutation	Baseline age >= 12 years N (%)	Total N (%)
Number of patients with genotype assessed		14	14
Deletions	[redacted]		
Insertions			
Inversions			
Substitution			
Other - [redacted]			
Other - [redacted] X [redacted]			

N: Number of patients, %: Percentage of patients.
Mutations are determined by either laboratory analysis carried out in the study or alternatively by post-hoc classification of gene defects reported in patients medical records where possible.
Note that some patients can have more than one mutation.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_geno.sas/14100130_genoage.txt

14.1.14 FVIII genotype by haemophilia severity at inclusion - full analysis set

Mutation	Submutation	Severe N (%)	Total N (%)
Number of patients with genotype assessed		14	14
Deletions	[redacted]		
Insertions			
Inversions			
Substitution			
Other - [redacted]			
Other - [redacted] X [redacted]			

N: Number of patients, %: Percentage of patients.
Severe: FVIII level <1%.
Mutations are determined by either laboratory analysis carried out in the study or alternatively by post-hoc classification of gene defects reported in patients medical records where possible.
Note that some patients can have more than one mutation.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_geno.sas/14100140_genofviii.txt

14.1.15 Family history of haemophilia by age at inclusion - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
History of relatives with haemophilia A (Y/N), N (%)			
N	14 (100.0)	54 (100.0)	68 (100.0)
Yes	9 (64.3)	32 (59.3)	41 (60.3)
No	5 (35.7)	20 (37.0)	25 (36.8)
Missing	-	2 (3.7)	2 (2.9)
Positive inhibitor test in relatives, N (%)			
N	14 (100.0)	54 (100.0)	68 (100.0)
Yes	-	6 (11.1)	6 (8.8)
No	5 (35.7)	21 (38.9)	26 (38.2)
Missing	9 (64.3)	27 (50.0)	36 (52.9)

N: Number of patients, %: Percentage of patients.
The family history is recalled by the patient or parents/LAR or physician.
LAR = Legally Acceptable Representative.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_famhaem.sas/14100150_genhistage.txt

14.1.16 Family history of haemophilia by haemophilia severity at inclusion - full analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
History of relatives with haemophilia A (Y/N), N (%)			
N	58 (100.0)	9 (100.0)	68 (100.0)
Yes	33 (56.9)	7 (77.8)	41 (60.3)
No	24 (41.4)	1 (11.1)	25 (36.8)
Missing	1 (1.7)	1 (11.1)	2 (2.9)
Positive inhibitor test in relatives, N (%)			
N	58 (100.0)	9 (100.0)	68 (100.0)
Yes	6 (10.3)	-	6 (8.8)
No	19 (32.8)	6 (66.7)	26 (38.2)
Missing	33 (56.9)	3 (33.3)	36 (52.9)

N: Number of patients, %: Percentage of patients.
Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
The family history is recalled by the patient or parents/LAR or physician.
LAR = Legally Acceptable Representative.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_famhaem.sas/14100160_genhistfviii.txt

14.1.17 Haemophilia treatment history by age at inclusion - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Current treatment prior to study, N (%)			
N	14 (100.0)	54 (100.0)	68 (100.0)
On-demand	-	5 (9.3)	5 (7.4)
Prophylaxis	14 (100.0)	49 (90.7)	63 (92.6)
Has the patient a history of switching FVIII products, N (%)			
N	14 (100.0)	53 (100.0)	67 (100.0)
Yes	6 (42.9)	45 (84.9)	51 (76.1)
No	4 (28.6)	5 (9.4)	9 (13.4)
NA	4 (28.6)	3 (5.7)	7 (10.4)
Prophylaxis/preventive regimen:			
Number of months on Prophylaxis			
N	13	48	61
Mean (SD)	27.2 (29.9)	22.8 (36.3)	23.7 (34.9)
Median	7.0	6.0	6.0
Min ; Max	4 ; 90	2 ; 192	2 ; 192
Average number of bleeds per month			
N	14	44	58
Mean (SD)	0.3 (0.5)	0.4 (0.7)	0.4 (0.6)
Median	0.2	0.2	0.2
Min ; Max	0 ; 2	0 ; 3	0 ; 3
Average number of bleeds per year			
N	14	44	58
Mean (SD)	3.2 (6.2)	5.3 (7.8)	4.8 (7.5)
Median	2.2	1.9	2.0
Min ; Max	0 ; 24	0 ; 31	0 ; 31
Current dose level (IU/kg)			
N	14	49	63
Mean (SD)	30.2 (12.1)	27.0 (12.2)	27.7 (12.1)
Median	28.7	26.6	28.3
Min ; Max	0 ; 50	5 ; 62	0 ; 62
Frequency of dosing, N (%)			
N	14 (100.0)	48 (100.0)	62 (100.0)
Once Weekly	1 (7.1)	5 (10.4)	6 (9.7)
Every 2nd day	1 (7.1)	10 (20.8)	11 (17.7)
3 times Weekly	11 (78.6)	23 (47.9)	34 (54.8)
Other	1 (7.1)	10 (20.8)	11 (17.7)
FVIII product given*, N (%)			
N	13 (100.0)	48 (100.0)	61 (100.0)
Plasma FVIII product	1 (7.7)	6 (12.5)	7 (11.5)
Recombinant FVIII	12 (92.3)	42 (87.5)	54 (88.5)

N: Number of patients, %: Percentage of patients.
NA: Not available, SD: Standard deviation.
Treatment history applies to the last 50 exposure days or the last 2 years (if 50 exposure days have not yet been reached) before switching to treatment with turoctocog alfa.
* Patients can consume more than one product.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_treathist.sas/14100170_treathistage.txt

Haemophilia treatment history by age at inclusion - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Documentation covering the last 50 exposure days/2 years, N (%)			
N	14 (100.0)	51 (100.0)	65 (100.0)
Diary	11 (78.6)	25 (49.0)	36 (55.4)
Patient Journal	2 (14.3)	8 (15.7)	10 (15.4)
Other	1 (7.1)	16 (31.4)	17 (26.2)
NA	-	2 (3.9)	2 (3.1)
On-demand regimen:			
Number of months On-demand regimen			
N	0	5	5
Mean (SD)	- (-)	33.6 (17.4)	33.6 (17.4)
Median	-	24.0	24.0
Min ; Max	- ; -	21 ; 63	21 ; 63
Average number of bleeds per month			
N	0	5	5
Mean (SD)	- (-)	1.9 (0.9)	1.9 (0.9)
Median	-	2.0	2.0
Min ; Max	- ; -	0 ; 3	0 ; 3
Average number of bleeds per year			
N	0	5	5
Mean (SD)	- (-)	22.6 (11.2)	22.6 (11.2)
Median	-	24.0	24.0
Min ; Max	- ; -	5 ; 36	5 ; 36
FVIII product given*, N (%)			
N	-	5 (100.0)	5 (100.0)
Recombinant FVIII	-	5 (100.0)	5 (100.0)
Documentation covering the last 50 exposure days/2 years, N (%)			
N	-	5 (100.0)	5 (100.0)
Diary	-	2 (40.0)	2 (40.0)
Patient Journal	-	2 (40.0)	2 (40.0)
Other	-	1 (20.0)	1 (20.0)
Surgeries:			
Any surgery within the last 5 yrs, N (%)			
N	14 (100.0)	53 (100.0)	67 (100.0)
Yes	6 (42.9)	29 (54.7)	35 (52.2)
No	8 (57.1)	24 (45.3)	32 (47.8)
Number of surgeries within the last 5 yrs			
N	6	28	34
Mean (SD)	1.0 (0.0)	1.6 (0.8)	1.5 (0.7)
Median	1.0	1.0	1.0
Min ; Max	1 ; 1	1 ; 3	1 ; 3

N: Number of patients, %: Percentage of patients.
NA: Not available, SD: Standard deviation.
Treatment history applies to the last 50 exposure days or the last 2 years (if 50 exposure days have not yet been reached) before switching to treatment with turoctocog alfa.
* Patients can consume more than one product.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_treathist.sas/14100170_treathistage.txt

Haemophilia treatment history by age at inclusion - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
FVIII prod during surgery*, N (%)			
N	6 (100.0)	43 (100.0)	49 (100.0)
Plasma FVIII product	-	7 (16.3)	7 (14.3)
Recombinant FVIII	6 (100.0)	36 (83.7)	42 (85.7)
Vaccinations:			
Number of vaccinations in the last 12 months			
N	12	36	48
Mean (SD)	0.3 (0.9)	0.1 (0.2)	0.1 (0.5)
Median	0.0	0.0	0.0
Min ; Max	0 ; 3	0 ; 1	0 ; 3

N: Number of patients, %: Percentage of patients.
NA: Not available, SD: Standard deviation.
Treatment history applies to the last 50 exposure days or the last 2 years (if 50 exposure days have not yet been reached) before switching to treatment with turoctocog alfa.
* Patients can consume more than one product.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_treathist.sas/14100170_treathistage.txt

14.1.18 Haemophilia treatment history by haemophilia severity at inclusion - full analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Current treatment prior to study, N (%)			
N	58 (100.0)	9 (100.0)	68 (100.0)
On-demand	3 (5.2)	1 (11.1)	5 (7.4)
Prophylaxis	55 (94.8)	8 (88.9)	63 (92.6)
Has the patient a history of switching FVIII products, N (%)			
N	57 (100.0)	9 (100.0)	67 (100.0)
Yes	42 (73.7)	8 (88.9)	51 (76.1)
No	8 (14.0)	1 (11.1)	9 (13.4)
NA	7 (12.3)	-	7 (10.4)
Prophylaxis/preventive regimen:			
Number of months on Prophylaxis			
N	53	8	61
Mean (SD)	21.8 (28.4)	36.3 (65.0)	23.7 (34.9)
Median	6.0	6.5	6.0
Min ; Max	2 ; 142	3 ; 192	2 ; 192
Average number of bleeds per month			
N	51	7	58
Mean (SD)	0.4 (0.6)	0.5 (0.8)	0.4 (0.6)
Median	0.2	0.0	0.2
Min ; Max	0 ; 3	0 ; 2	0 ; 3
Average number of bleeds per year			
N	51	7	58
Mean (SD)	4.6 (7.3)	5.9 (9.0)	4.8 (7.5)
Median	2.0	0.1	2.0
Min ; Max	0 ; 31	0 ; 20	0 ; 31
Current dose level (IU/kg)			
N	55	8	63
Mean (SD)	28.2 (12.2)	24.1 (11.7)	27.7 (12.1)
Median	28.3	22.4	28.3
Min ; Max	0 ; 62	11 ; 39	0 ; 62
Frequency of dosing, N (%)			
N	55 (100.0)	7 (100.0)	62 (100.0)
Once Weekly	5 (9.1)	1 (14.3)	6 (9.7)
Every 2nd day	9 (16.4)	2 (28.6)	11 (17.7)
3 times Weekly	30 (54.5)	4 (57.1)	34 (54.8)
Other	11 (20.0)	-	11 (17.7)
FVIII product given*, N (%)			
N	53 (100.0)	8 (100.0)	61 (100.0)
Plasma FVIII product	5 (9.4)	2 (25.0)	7 (11.5)
Recombinant FVIII	48 (90.6)	6 (75.0)	54 (88.5)

N: Number of patients, %: Percentage of patients.
NA: Not available, SD: Standard deviation.
Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
Treatment history applies to the last 50 exposure days or the last 2 years (if 50 exposure days have not yet been reached) before switching to treatment with turoctocog alfa.
* Patients can consume more than one product.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_treathist.sas/14100180_treathistfviii.txt

Haemophilia treatment history by haemophilia severity at inclusion - full analysis set

	Severe	Moderately Severe	Total
Documentation covering the last 50 exposure days/2 years, N (%)			
N	56 (100.0)	9 (100.0)	65 (100.0)
Diary	32 (57.1)	4 (44.4)	36 (55.4)
Patient Journal	9 (16.1)	1 (11.1)	10 (15.4)
Other	14 (25.0)	3 (33.3)	17 (26.2)
NA	1 (1.8)	1 (11.1)	2 (3.1)
On-demand regimen:			
Number of months On-demand regimen			
N	3	1	5
Mean (SD)	41.0 (20.0)	24.0 (-)	33.6 (17.4)
Median	36.0	24.0	24.0
Min ; Max	24 ; 63	24 ; 24	21 ; 63
Average number of bleeds per month			
N	3	1	5
Mean (SD)	1.5 (0.9)	3.0 (-)	1.9 (0.9)
Median	2.0	3.0	2.0
Min ; Max	0 ; 2	3 ; 3	0 ; 3
Average number of bleeds per year			
N	3	1	5
Mean (SD)	17.6 (11.0)	36.0 (-)	22.6 (11.2)
Median	24.0	36.0	24.0
Min ; Max	5 ; 24	36 ; 36	5 ; 36
FVIII product given*, N (%)			
N	3 (100.0)	1 (100.0)	5 (100.0)
Recombinant FVIII	3 (100.0)	1 (100.0)	5 (100.0)
Documentation covering the last 50 exposure days/2 years, N (%)			
N	3 (100.0)	1 (100.0)	5 (100.0)
Diary	2 (66.7)	-	2 (40.0)
Patient Journal	1 (33.3)	1 (100.0)	2 (40.0)
Other	-	-	1 (20.0)
Surgeries:			
Any surgery within the last 5 yrs, N (%)			
N	57 (100.0)	9 (100.0)	67 (100.0)
Yes	29 (50.9)	5 (55.6)	35 (52.2)
No	28 (49.1)	4 (44.4)	32 (47.8)
Number of surgeries within the last 5 yrs			
N	29	4	34
Mean (SD)	1.4 (0.7)	2.3 (1.0)	1.5 (0.7)
Median	1.0	2.5	1.0
Min ; Max	1 ; 3	1 ; 3	1 ; 3

N: Number of patients, %: Percentage of patients.
NA: Not available, SD: Standard deviation.
Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
Treatment history applies to the last 50 exposure days or the last 2 years (if 50 exposure days have not yet been reached) before switching to treatment with turoctocog alfa.
* Patients can consume more than one product.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_treathist.sas/14100180_treathistfviii.txt

Haemophilia treatment history by haemophilia severity at inclusion - full analysis set

	Severe	Moderately Severe	Total
FVIII prod during surgery*, N (%)			
N	37 (100.0)	10 (100.0)	49 (100.0)
Plasma FVIII product	6 (16.2)	-	7 (14.3)
Recombinant FVIII	31 (83.8)	10 (100.0)	42 (85.7)
Vaccinations:			
Number of vaccinations in the last 12 months			
N	40	7	48
Mean (SD)	0.2 (0.5)	0.0 (0.0)	0.1 (0.5)
Median	0.0	0.0	0.0
Min ; Max	0 ; 3	0 ; 0	0 ; 3

N: Number of patients, %: Percentage of patients.
NA: Not available, SD: Standard deviation.
Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
Treatment history applies to the last 50 exposure days or the last 2 years (if 50 exposure days have not yet been reached) before switching to treatment with turoctocog alfa.
* Patients can consume more than one product.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1410_treathist.sas/14100180_treathistfviii.txt

14.2 Efficacy data

14.2.1 Patient disposition by age at inclusion - all patients

	Baseline age < 12 years	Baseline age >= 12 years	Total
Screened			70
Included in study	14 (100.0)	55 (100.0)	69 (100.0)
Withdrawn	5 (35.7)	6 (10.9)	11 (15.9)
Protocol Violation	1 (7.1)	0 (0.0)	1 (1.4)
Withdrawal By Subject	0 (0.0)	6 (10.9)	6 (8.7)
Other	4 (28.6)	0 (0.0)	4 (5.8)
Completed study	9 (64.3)	49 (89.1)	58 (84.1)
Full analysis set	14 (100.0)	54 (98.2)	68 (98.6)
Prophylactic regimen	14 (100.0)	49 (89.1)	63 (91.3)
On-demand regimen	0 (0.0)	5 (9.1)	5 (7.2)
Safety analysis set	14 (100.0)	54 (98.2)	68 (98.6)
Number of visits	40	248	288
Years in study*	12.5	75.2	87.8
Prophylactic regimen	12.5	63.5	76.0
On-demand regimen	0	11.7	11.7
EDs in study*	1825	7142	8967
Undergone surgery during study	1 (7.1)	7 (12.7)	8 (11.6)
Completed study with <100ED**	0 (0.0)	8 (14.5)	8 (11.6)

The full analysis set and the safety analysis set both consists of all patients exposed to FVIII during study participation.
* The sum for all patients in FAS, across all visits, is presented. ED: Exposure day.
**Principal Investigator has confirmed and signed that although the patients recorded less than 100EDs have completed the study.

nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_patdisp.sas/14200010_subj_dispage.txt

14.2.2 Patient disposition by haemophilia severity at inclusion - all patients

	Severe	Moderately Severe	Total
Screened			70
Included in study by severity+	58 (100.0)	10 (100.0)	69 (100.0)
Withdrawn	8 (13.8)	3 (30.0)	11 (15.9)
Protocol Violation	0 (0.0)	1 (10.0)	1 (1.4)
Withdrawal By Subject	4 (6.9)	2 (20.0)	6 (8.7)
Other	4 (6.9)	0 (0.0)	4 (5.8)
Completed study	50 (86.2)	7 (70.0)	58 (84.1)
Full analysis set	58 (100.0)	9 (90.0)	68 (98.6)
Prophylactic regimen	55 (94.8)	8 (80.0)	63 (91.3)
On-demand regimen	3 (5.2)	1 (10.0)	5 (7.2)
Safety analysis set	58 (100.0)	9 (90.0)	68 (98.6)
Number of visits	248	37	288
Years in study*	76.3	10.4	87.8
Prophylactic regimen	67.3	8.7	76.0
On-demand regimen	9.0	1.7	11.7
EDs in study*	7932	991	8967
Undergone surgery during study	4 (6.9)	3 (30.0)	8 (11.6)
Completed study with <100ED**	6 (10.3)	1 (10.0)	8 (11.6)

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
+ 1 patient with FVIII activity >2% at inclusion is included in the 'Total' column
to represent the full analysis set.
The full analysis set and the safety analysis set both consists of all patients exposed to FVIII during study participation.
* The sum for all patients in FAS, across all visits, is presented. ED: Exposure day.
**Principal Investigator has confirmed and signed that although the patients recorded less than 100EDs have completed the study.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_patdisp.sas/14200020_subj_dispfviii.txt

14.2.3 Patient disposition by age at inclusion - completers

	Baseline age < 12 years	Baseline age >= 12 years	Total
Screened			70
Completed study	9 (100.0)	49 (100.0)	58 (100.0)
Full analysis set	9 (100.0)	49 (100.0)	58 (100.0)
Prophylactic regimen	9 (100.0)	44 (89.8)	53 (91.4)
On-demand regimen	0 (0.0)	5 (10.2)	5 (8.6)
Safety analysis set	9 (100.0)	49 (100.0)	58 (100.0)
Number of visits	30	232	262
Years in study*	10.5	71.6	82.1
Prophylactic regimen	10.5	59.9	70.4
On-demand regimen	0	11.7	11.7
EDs in study*	1604	6835	8439
Undergone surgery during study	1 (11.1)	7 (14.3)	8 (13.8)
Completed study with <100ED**	0 (0.0)	8 (16.3)	8 (13.8)

The full analysis set and the safety analysis set both consists of all patients exposed to FVIII during study participation.
* The sum for all patients in FAS, across all visits, is presented. ED: Exposure day.
**Principal Investigator has confirmed and signed that although the patients recorded less than 100EDs have completed the study.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_patdisp.sas/14200021_subj_dispcompl.txt

14.2.4 Patient disposition by age at inclusion - non-completers

	Baseline age < 12 years	Baseline age >= 12 years	Total
Screened			70
Withdrawn	5 (100.0)	6 (100.0)	11 (100.0)
Protocol Violation	1 (20.0)	0 (0.0)	1 (9.1)
Withdrawal By Subject	0 (0.0)	6 (100.0)	6 (54.5)
Other	4 (80.0)	0 (0.0)	4 (36.4)
Full analysis set	5 (100.0)	5 (83.3)	10 (90.9)
Prophylactic regimen	5 (100.0)	5 (83.3)	10 (90.9)
Safety analysis set	5 (100.0)	5 (83.3)	10 (90.9)
Number of visits	10	16	26
Years in study*	2.0	3.7	5.7
Prophylactic regimen	2.0	3.7	5.7
EDs in study*	221	307	528

The full analysis set and the safety analysis set both consists of all patients exposed to FVIII during study participation.
* The sum for all patients in FAS, across all visits, is presented. ED: Exposure day.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_patdisp.sas/14200022_subj_dispnoncompl.txt

14.2.5 Consumption of FVIII during the study by age at inclusion - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Total consumption of turoctocog alfa* per patient per month** (IU/kg BW/month)			
N	14	54	68
Mean (SD)	391.2 (141.3)	287.7 (198.4)	309.0 (191.8)
Median	351.0	277.4	320.3
Min ; Max	155.2 ; 653.5	10.8 ; 853.2	10.8 ; 853.2
Consumption of turoctocog alfa for prophylaxis per patient per month+ (IU/kg BW/month)			
N	14	49	63
Mean (SD)	376.1 (139.8)	282.0 (167.1)	302.9 (165.1)
Median	350.8	283.3	301.2
Min ; Max	155.2 ; 649.6	5.3 ; 656.0	5.3 ; 656.0
Consumption of turoctocog alfa per bleed*** (IU/kg BW/bleed)			
N	32	436	468
Mean (SD)	70.9 (60.5)	57.1 (101.2)	58.0 (99.0)
Median	47.2	31.0	31.3
Min ; Max	23.8 ; 250.0	7.7 ; 1244.4	7.7 ; 1244.4
Consumption of turoctocog alfa for surgery++ (IU/kg BW)			
N	0	7	7
Mean (SD)	- (-)	145.9 (171.6)	145.9 (171.6)
Median	-	88.4	88.4
Min ; Max	- ; -	12.5 ; 497.1	12.5 ; 497.1
Average dose of turoctocog alfa for prophylaxis per patient per exposure day+ (IU/kg BW/ED)			
N	14	49	63
Mean (SD)	33.0 (9.3)	29.2 (11.9)	30.1 (11.4)
Median	29.6	29.7	29.7
Min ; Max	22.3 ; 55.3	9.9 ; 57.3	9.9 ; 57.3
Average dose of turoctocog alfa per bleed per injection*** (IU/kg BW/bleed)			
N	32	436	468
Mean (SD)	31.2 (12.6)	23.3 (10.1)	23.8 (10.4)
Median	27.3	23.8	24.1
Min ; Max	15.2 ; 62.5	5.4 ; 55.6	5.4 ; 62.5

SD: Standard deviation.
* Consumption includes all doses given for prophylaxis, treatment of bleed or surgery.
** N is number of patients with more than one exposure day reported.
*** N is number of bleeds.
+ N is number of patients on prophylaxis/preventive regimen with more than one exposure day reported
++ N is number of patients with surgeries requiring treatment with turoctocog alfa.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_cons.sas/14200030_consage.txt

14.2.6 Consumption of FVIII during the study by haemophilia severity at inclusion - full analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Total consumption of turoctocog alfa* per patient per month** (IU/kg BW/month)			
N	58	9	68
Mean (SD)	312.0 (162.9)	316.8 (333.4)	309.0 (191.8)
Median	327.8	155.2	320.3
Min ; Max	10.8 ; 687.7	27.8 ; 853.2	10.8 ; 853.2
Consumption of turoctocog alfa for prophylaxis per patient per month+ (IU/kg BW/month)			
N	55	8	63
Mean (SD)	307.4 (155.8)	271.8 (230.2)	302.9 (165.1)
Median	312.1	167.5	301.2
Min ; Max	5.3 ; 656.0	21.6 ; 650.5	5.3 ; 656.0
Consumption of turoctocog alfa per bleed*** (IU/kg BW/bleed)			
N	411	50	468
Mean (SD)	46.8 (49.5)	147.4 (246.7)	58.0 (99.0)
Median	31.3	26.1	31.3
Min ; Max	7.7 ; 525.0	12.5 ; 1244.4	7.7 ; 1244.4
Consumption of turoctocog alfa for surgery++ (IU/kg BW)			
N	3	3	7
Mean (SD)	224.8 (243.7)	43.9 (39.6)	145.9 (171.6)
Median	150.0	30.8	88.4
Min ; Max	27.2 ; 497.1	12.5 ; 88.4	12.5 ; 497.1
Average dose of turoctocog alfa for prophylaxis per patient per exposure day+ (IU/kg BW/ED)			
N	55	8	63
Mean (SD)	30.3 (11.2)	28.5 (13.5)	30.1 (11.4)
Median	29.8	26.3	29.7
Min ; Max	9.9 ; 57.3	10.4 ; 50.3	9.9 ; 57.3
Average dose of turoctocog alfa per bleed per injection*** (IU/kg BW/bleed)			
N	411	50	468
Mean (SD)	23.5 (10.3)	28.8 (8.9)	23.8 (10.4)
Median	23.8	26.1	24.1
Min ; Max	6.4 ; 62.5	12.5 ; 50.3	5.4 ; 62.5

SD: Standard deviation.
Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
* Consumption includes all doses given for prophylaxis, treatment of bleed or surgery.
** N is number of patients with more than one exposure day reported.
*** N is number of bleeds.
+ N is number of patients on prophylaxis/preventive regimen with more than one exposure day reported
++ N is number of patients with surgeries requiring treatment with turoctocog alfa.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_cons.sas/14200040_consfviii.txt

14.2.7 Details of bleeding episodes by age at inclusion - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of bleeding episodes	32	437	469
Number of patients with bleeds	8	38	46
Cause of bleed, N (%)			
N	32 (100.0)	437 (100.0)	469 (100.0)
Spontaneous	8 (25.0)	300 (68.6)	308 (65.7)
Traumatic	24 (75.0)	79 (18.1)	103 (22.0)
Unknown	-	58 (13.3)	58 (12.4)
Location of bleed, N (%)			
N	32 (100.0)	437 (100.0)	469 (100.0)
Joint	18 (56.3)	309 (70.7)	327 (69.7)
Gastrointestinal	-	2 (0.5)	2 (0.4)
Mucosal	-	10 (2.3)	10 (2.1)
Muscular	3 (9.4)	48 (11.0)	51 (10.9)
Subcutaneous	4 (12.5)	21 (4.8)	25 (5.3)
Other	7 (21.9)	43 (9.8)	50 (10.7)
Unknown	-	4 (0.9)	4 (0.9)
Therapy other than haemostatic drug, N (%)			
N	32 (100.0)	437 (100.0)	469 (100.0)
Compression	1 (3.1)	3 (0.7)	4 (0.9)
Ice	5 (15.6)	35 (8.0)	40 (8.5)
Other	-	12 (2.7)	12 (2.6)
Not Used	-	37 (8.5)	37 (7.9)
None	-	1 (0.2)	1 (0.2)
Unknown	26 (81.3)	349 (79.9)	375 (80.0)
Severity of bleed, N (%)			
N	32 (100.0)	437 (100.0)	469 (100.0)
Mild/Moderate	27 (84.4)	360 (82.4)	387 (82.5)
Severe	1 (3.1)	12 (2.7)	13 (2.8)
Unknown	4 (12.5)	65 (14.9)	69 (14.7)

N: Number of bleeds, %: Percentage of bleeds
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_bleed_details.sas/14200050_bl_detailsage.txt

14.2.8 Details of bleeding episodes by haemophilia severity at inclusion - full analysis set

	Severe	Moderately Severe	Total
Number of bleeding episodes	412	50	469
Number of patients with bleeds	39	6	46
Cause of bleed, N (%)			
N	412 (100.0)	50 (100.0)	469 (100.0)
Spontaneous	283 (68.7)	19 (38.0)	308 (65.7)
Traumatic	97 (23.5)	5 (10.0)	103 (22.0)
Unknown	32 (7.8)	26 (52.0)	58 (12.4)
Location of bleed, N (%)			
N	412 (100.0)	50 (100.0)	469 (100.0)
Joint	294 (71.4)	29 (58.0)	327 (69.7)
Gastrointestinal	2 (0.5)	-	2 (0.4)
Mucosal	10 (2.4)	-	10 (2.1)
Muscular	38 (9.2)	11 (22.0)	51 (10.9)
Subcutaneous	23 (5.6)	2 (4.0)	25 (5.3)
Other	42 (10.2)	7 (14.0)	50 (10.7)
Unknown	3 (0.7)	1 (2.0)	4 (0.9)
Therapy other than haemostatic drug, N (%)			
N	412 (100.0)	50 (100.0)	469 (100.0)
Compression	3 (0.7)	-	4 (0.9)
Ice	38 (9.2)	2 (4.0)	40 (8.5)
Other	10 (2.4)	2 (4.0)	12 (2.6)
Not Used	37 (9.0)	-	37 (7.9)
None	1 (0.2)	-	1 (0.2)
Unknown	323 (78.4)	46 (92.0)	375 (80.0)
Severity of bleed, N (%)			
N	412 (100.0)	50 (100.0)	469 (100.0)
Mild/Moderate	335 (81.3)	45 (90.0)	387 (82.5)
Severe	9 (2.2)	4 (8.0)	13 (2.8)
Unknown	68 (16.5)	1 (2.0)	69 (14.7)

N: Number of bleeds, %: Percentage of bleeds
Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_bleed_details.sas/14200060_bl_detailsfviii.txt

14.2.9 Number of Injections of turoctocog alfa per bleeding episode by age at inclusion - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of Patients	14	54	68
Number of Patients with bleeding episodes, N*(%)	8(57.1)	38(70.4)	46(67.6)
Injections to treat the bleed,from start to stop of the bleed, N(%)			
N	32(100.0)	437(100.0)	469(100.0)
1 injection	12(37.5)	222(50.8)	234(49.9)
2 injections	12(37.5)	87(19.9)	99(21.1)
3 injections	2(6.3)	66(15.1)	68(14.5)
4 injections	1(3.1)	19(4.3)	20(4.3)
5 injections	4(12.5)	9(2.1)	13(2.8)
6 injections	1(3.1)	10(2.3)	11(2.3)
7 injections	-	2(0.5)	2(0.4)
8 injections	-	5(1.1)	5(1.1)
9 injections	-	2(0.5)	2(0.4)
10 injections	-	3(0.7)	3(0.6)
11 injections	-	3(0.7)	3(0.6)
12 injections	-	1(0.2)	1(0.2)
14 injections	-	1(0.2)	1(0.2)
16 injections	-	1(0.2)	1(0.2)
17 injections	-	1(0.2)	1(0.2)
20 injections	-	1(0.2)	1(0.2)
21 injections	-	1(0.2)	1(0.2)
22 injections	-	1(0.2)	1(0.2)
48 injections	-	1(0.2)	1(0.2)
69 injections	-	1(0.2)	1(0.2)
Injection to stop the bleed			
N	32	437	469
Mean (SD)	2.25 (1.48)	2.63 (4.68)	2.60 (4.53)
Median(IQR)	2.00 (1.50)	1.00 (2.00)	2.00 (2.00)
Min ; Max	1.00 ;6.00	1.00 ;69.00	1.00 ;69.00

N*: Number of Patients, N: Number of bleeds
SD: Standard deviation, IQR: Interquartile Range
Number of Infusions to Treat the Bleed is calculated as the number of infusions of turoctucog alfa given per patient and bleed which includes all doses given between start and stop date of the bleed.

nn7008-3553/ctr_20201215_er - 15DEC2020 - t_postrm_infusion_n8.sas/t_postrm_infusion_n8_age.txt

14.2.10 Number of Injections of turoctocog alfa per bleeding episode by haemophilia severity at inclusion - full analysis set

	Severe	Moderately Severe	Total
Number of Patients	58	9	68
Number of Patients with bleeding episodes, N*(%)	39(67.2)	6(66.7)	46(67.6)
Injections to treat the bleed,from start to stop of the bleed, N(%)			
N	412(100.0)	50(100.0)	469(100.0)
1 injection	206(50.0)	28(56.0)	234(49.9)
2 injections	93(22.6)	3(6.0)	99(21.1)
3 injections	63(15.3)	2(4.0)	68(14.5)
4 injections	16(3.9)	4(8.0)	20(4.3)
5 injections	11(2.7)	2(4.0)	13(2.8)
6 injections	9(2.2)	2(4.0)	11(2.3)
7 injections	1(0.2)	1(2.0)	2(0.4)
8 injections	3(0.7)	2(4.0)	5(1.1)
9 injections	2(0.5)	-	2(0.4)
10 injections	3(0.7)	-	3(0.6)
11 injections	3(0.7)	-	3(0.6)
12 injections	-	1(2.0)	1(0.2)
14 injections	1(0.2)	-	1(0.2)
16 injections	-	1(2.0)	1(0.2)
17 injections	1(0.2)	-	1(0.2)
20 injections	-	1(2.0)	1(0.2)
21 injections	-	1(2.0)	1(0.2)
22 injections	-	1(2.0)	1(0.2)
48 injections	-	1(2.0)	1(0.2)
69 injections	-	-	1(0.2)
Injection to stop the bleed			
N	412	50	469
Mean (SD)	2.18 (1.97)	4.80 (8.20)	2.60 (4.53)
Median(IQR)	1.50 (2.00)	1.00 (4.00)	2.00 (2.00)
Min ; Max	1.00 ;17.00	1.00 ;48.00	1.00 ;69.00

N*: Number of Patients, N: Number of bleeds
SD: Standard deviation, IQR: Interquartile Range
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
Number of Infusions to Treat the Bleed is calculated as the number of infusions of turoctucog alfa given per patient and bleed which includes all doses given between start and stop date of the bleed.

nn7008-3553/ctr_20201215_er - 15DEC2020 - t_postrm_infusion_n8.sas/t_postrm_infusion_n8_sev.txt

14.2.11 Haemostatic effect of turoctocog alfa in the treatment of bleeds by age at inclusion - excluding missing responses - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Number of patients with bleeding episodes*	7	30	37
Number of bleeding episodes	23	338	361
Haemostatic response, N (%)			
N	23 (100.0)	338 (100.0)	361 (100.0)
Excellent	15 (65.2)	77 (22.8)	92 (25.5)
Good	8 (34.8)	215 (63.6)	223 (61.8)
Moderate	-	37 (10.9)	37 (10.2)
None	-	9 (2.7)	9 (2.5)
Success rate, N (%)			
N	23 (100.0)	338 (100.0)	361 (100.0)
Success	23 (100.0)	292 (86.4)	315 (87.3)
Failure	-	46 (13.6)	46 (12.7)

N: Number of bleeds, %: Percentage of bleeds
Success is defined as either Excellent or Good. Failure is defined as either Moderate or None.
* Number of patients with bleeding episodes using NN diary where haemostatic response is collected.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_haemeff.sas/14200070_haemeff_age1.txt

14.2.12 Haemostatic effect of turoctocog alfa in the treatment of bleeds by haemophilia severity at inclusion - excluding missing responses - full analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Number of patients with bleeding episodes*	31	5	37
Number of bleeding episodes	331	23	361
Haemostatic response, N (%)			
N	331 (100.0)	23 (100.0)	361 (100.0)
Excellent	84 (25.4)	2 (8.7)	92 (25.5)
Good	207 (62.5)	15 (65.2)	223 (61.8)
Moderate	32 (9.7)	5 (21.7)	37 (10.2)
None	8 (2.4)	1 (4.3)	9 (2.5)
Success rate, N (%)			
N	331 (100.0)	23 (100.0)	361 (100.0)
Success	291 (87.9)	17 (73.9)	315 (87.3)
Failure	40 (12.1)	6 (26.1)	46 (12.7)

N: Number of bleeds, %: Percentage of bleeds
Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column
to represent the full analysis set.
Success is defined as either Excellent or Good. Failure is defined as either Moderate or None.
* Number of patients with bleeding episodes using NN diary where haemostatic response is collected.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_haemeff.sas/14200080_haemeff_fviii1.txt

14.2.13 Haemostatic effect of turoctocog alfa in the treatment of bleeds by age at inclusion - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Number of patients with bleeding episodes*	7	32	39
Number of bleeding episodes	25	399	424
Haemostatic response, N (%)			
N	25 (100.0)	399 (100.0)	424 (100.0)
Excellent	15 (60.0)	77 (19.3)	92 (21.7)
Good	8 (32.0)	215 (53.9)	223 (52.6)
Moderate	-	37 (9.3)	37 (8.7)
None	-	9 (2.3)	9 (2.1)
Missing	2 (8.0)	61 (15.3)	63 (14.9)
Success rate, N (%)			
N	25 (100.0)	399 (100.0)	424 (100.0)
Success	23 (92.0)	292 (73.2)	315 (74.3)
Failure	2 (8.0)	107 (26.8)	109 (25.7)

N: Number of bleeds, %: Percentage of bleeds
Success is defined as either Excellent or Good. Failure is defined as either Moderate or None or if the response is missing.
* Number of patients with bleeding episodes using NN diary where haemostatic response is collected.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_haemeff.sas/14200090_haemeff_age.txt

14.2.14 Haemostatic effect of turoctocog alfa in the treatment of bleeds by haemophilia severity at inclusion - full analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Number of patients with bleeding episodes*	32	6	39
Number of bleeding episodes	367	50	424
Haemostatic response, N (%)			
N	367 (100.0)	50 (100.0)	424 (100.0)
Excellent	84 (22.9)	2 (4.0)	92 (21.7)
Good	207 (56.4)	15 (30.0)	223 (52.6)
Moderate	32 (8.7)	5 (10.0)	37 (8.7)
None	8 (2.2)	1 (2.0)	9 (2.1)
Missing	36 (9.8)	27 (54.0)	63 (14.9)
Success rate, N (%)			
N	367 (100.0)	50 (100.0)	424 (100.0)
Success	291 (79.3)	17 (34.0)	315 (74.3)
Failure	76 (20.7)	33 (66.0)	109 (25.7)

N: Number of bleeds, %: Percentage of bleeds
Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
Success is defined as either Excellent or Good. Failure is defined as either Moderate or None or if the response is missing.
* Number of patients with bleeding episodes using NN diary where haemostatic response is collected.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_haemeff.sas/14200100_haemeff_fviii.txt

14.2.15 Haemostatic effect of turoctocog alfa during surgical procedures by age at inclusion - excluding missing responses - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Number of patients who had surgery*	1	5	6
Number of surgeries	2	5	7
Haemostatic response, N (%)			
N	2 (100.0)	5 (100.0)	7 (100.0)
Excellent	2 (100.0)	3 (60.0)	5 (71.4)
Good	-	2 (40.0)	2 (28.6)
Moderate	-	-	-
None	-	-	-
Success rate, N (%)			
N	2 (100.0)	5 (100.0)	7 (100.0)
Success	2 (100.0)	5 (100.0)	7 (100.0)
Failure	-	-	-

N: Number of surgeries, %: Percentage of surgeries
Success is defined as either Excellent or Good. Failure is defined as either Moderate or None.
* Number of patients who had surgery requiring additional treatment with turoctocog alfa.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_haemeff.sas/14200110_haemeffs_age1.txt

14.2.16 Haemostatic effect of turoctocog alfa during surgical procedures by haemophilia severity at inclusion - excluding missing responses - full analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Number of patients who had surgery*	3	2	6
Number of surgeries	4	2	7
Haemostatic response, N (%)			
N	4 (100.0)	2 (100.0)	7 (100.0)
Excellent	4 (100.0)	-	5 (71.4)
Good	-	2 (100.0)	2 (28.6)
Moderate	-	-	-
None	-	-	-
Success rate, N (%)			
N	4 (100.0)	2 (100.0)	7 (100.0)
Success	4 (100.0)	2 (100.0)	7 (100.0)
Failure	-	-	-

N: Number of surgeries, %: Percentage of surgeries
Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
Success is defined as either Excellent or Good. Failure is defined as either Moderate or None.
* Number of patients who had surgery requiring additional treatment with turoctocog alfa.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_haemeff.sas/14200120_haemeffs_fviii1.txt

14.2.17 Haemostatic effect of turoctocog alfa during surgical procedures by age at inclusion - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Number of patients who had surgery*	1	7	8
Number of surgeries	2	9	11
Haemostatic response, N (%)			
N	2 (100.0)	9 (100.0)	11 (100.0)
Excellent	2 (100.0)	3 (33.3)	5 (45.5)
Good	-	2 (22.2)	2 (18.2)
Moderate	-	-	-
None	-	-	-
Missing	-	4 (44.4)	4 (36.4)
Success rate, N (%)			
N	2 (100.0)	9 (100.0)	11 (100.0)
Success	2 (100.0)	5 (55.6)	7 (63.6)
Failure	-	4 (44.4)	4 (36.4)

N: Number of surgeries, %: Percentage of surgeries
Success is defined as either Excellent or Good. Failure is defined as either Moderate or None or if the response is missing.
* Number of patients who had surgery requiring additional treatment with turoctocog alfa.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_haemeff.sas/14200130_haemeffs_age.txt

14.2.18 Haemostatic effect of turoctocog alfa during surgical procedures by haemophilia severity at inclusion - full analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Number of patients who had surgery*	4	3	8
Number of surgeries	6	4	11
Haemostatic response, N (%)			
N	6 (100.0)	4 (100.0)	11 (100.0)
Excellent	4 (66.7)	-	5 (45.5)
Good	-	2 (50.0)	2 (18.2)
Moderate	-	-	-
None	-	-	-
Missing	2 (33.3)	2 (50.0)	4 (36.4)
Success rate, N (%)			
N	6 (100.0)	4 (100.0)	11 (100.0)
Success	4 (66.7)	2 (50.0)	7 (63.6)
Failure	2 (33.3)	2 (50.0)	4 (36.4)

N: Number of surgeries, %: Percentage of surgeries
Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
Success is defined as either Excellent or Good. Failure is defined as either Moderate or None or if the response is missing.
* Number of patients who had surgery requiring additional treatment with turoctocog alfa.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_haemeff.sas/14200140_haemeffs_fviii.txt

14.2.19 Haemostatic effect of turoctocog alfa in the treatment of bleeds by severity of bleeding episode - excluding missing responses - full analysis set

	Severe	Mild/Moderate	Total
Number of patients with bleeding episodes*	10	35	37
Number of bleeding episodes	13	347	360
Haemostatic response, N (%)			
N	13 (100.0)	347 (100.0)	360 (100.0)
Excellent	1 (7.7)	91 (26.2)	92 (25.6)
Good	7 (53.8)	215 (62.0)	222 (61.7)
Moderate	3 (23.1)	34 (9.8)	37 (10.3)
None	2 (15.4)	7 (2.0)	9 (2.5)
Success rate, N (%)			
N	13 (100.0)	347 (100.0)	360 (100.0)
Success	8 (61.5)	306 (88.2)	314 (87.2)
Failure	5 (38.5)	41 (11.8)	46 (12.8)

N: Number of bleeds, %: Percentage of bleeds
Success is defined as either Excellent or Good. Failure is defined as either Moderate or None.
Bleeding episodes with missing severity have been excluded.
* Number of patients with bleeding episodes using NN diary where haemostatic response is collected.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_haemeff.sas/14200141_haemeff_beclass.txt

14.2.20 Annualised bleeding rate by age at inclusion - patients on prophylaxis regimen - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	49	63
N*	14	48	62
Number of patients with bleeds	8 (57.1)	32 (66.7)	40 (64.5)
Total number of bleeds	32	208	240
Mean bleeds per patient	2.29	4.33	3.87
Median bleeds per patient	1.50	2.00	2.00
Range of bleeds, min ; max	0 ; 7	0 ; 40	0 ; 40
Mean observation period (years)	0.89	1.24	1.17
Observation period, min ; max, (years)	0.21 ; 1.71	0.21 ; 5.06	0.21 ; 5.06
Total observation period (years)	12.52	59.73	72.25
Negative binomial analysis			
Annualised bleeding rate	2.75	3.90	3.65
95% CI	(1.35, 5.61)	(2.57, 5.92)	(2.53, 5.25)
Poisson analysis			
Annualised bleeding rate	2.56	3.48	3.32
95% CI	(1.36, 4.82)	(2.29, 5.29)	(2.31, 4.78)
Annualised bleeding rate, summary			
Mean (SD)	2.70 (3.52)	3.96 (5.19)	3.67 (4.87)
Median (IQR)	1.34 (4.02)	2.14 (6.56)	1.97 (6.19)
Min ; Max	0.00 ; 9.99	0.00 ; 25.50	0.00 ; 25.50

CI: Confidence interval, SD: Standard deviation, IQR: Interquartile Range
A 95% CI for the annualised bleeding rate is estimated from a negative binomial model, with a sensitivity analysis using a Poisson model allowing for over-dispersion. If the number of patients per subgroup is less than 2, only the Poisson estimate of rate is provided.
* Number of patients with more than one exposure day reported, only these patients are included in the analysis.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_bleed_rate.sas/14200150_bl_rate_page.txt

14.2.21 Annualised bleeding rate by haemophilia severity at inclusion - patients on prophylaxis regimen - full analysis set

	Severe	Moderately Severe	Total
Number of patients	55	8	63
N*	54	8	62
Number of patients with bleeds	35 (64.8)	5 (62.5)	40 (64.5)
Total number of bleeds	217	23	240
Mean bleeds per patient	4.02	2.88	3.87
Median bleeds per patient	2.00	2.50	2.00
Range of bleeds, min ; max	0 ; 40	0 ; 8	0 ; 40
Mean observation period (years)	1.20	0.96	1.17
Observation period, min ; max, (years)	0.21 ; 5.06	0.21 ; 1.97	0.21 ; 5.06
Total observation period (years)	64.61	7.64	72.25
Negative binomial analysis			
Annualised bleeding rate	3.67	3.37	3.65
95% CI	(2.47, 5.46)	(1.41, 8.06)	(2.53, 5.25)
Poisson analysis			
Annualised bleeding rate	3.36	3.01	3.32
95% CI	(2.25, 5.00)	(1.43, 6.36)	(2.31, 4.78)
Annualised bleeding rate, summary			
Mean (SD)	3.67 (5.01)	3.69 (4.05)	3.67 (4.87)
Median (IQR)	1.93 (6.19)	2.76 (7.04)	1.97 (6.19)
Min ; Max	0.00 ; 25.50	0.00 ; 9.91	0.00 ; 25.50

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
CI: Confidence interval, SD: Standard deviation, IQR: Interquartile Range
A 95% CI for the annualised bleeding rate is estimated from a negative binomial model, with a sensitivity analysis using a Poisson model allowing for over-dispersion. If the number of patients per subgroup is less than 2, only the Poisson estimate of rate is provided.
* Number of patients with more than one exposure day reported, only these patients are included in the analysis.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_bleed_rate.sas/14200160_bl_rate_pfviii.txt

14.2.22 Annualised bleeding rate by age at inclusion - patients on on-demand regimen - full analysis set

	Baseline age >= 12 years	Total
Number of patients	5	5
N*	5	5
Number of patients with bleeds	5 (100.0)	5 (100.0)
Total number of bleeds	228	228
Mean bleeds per patient	45.60	45.60
Median bleeds per patient	37.00	37.00
Range of bleeds, min ; max	7 ; 101	7 ; 101
Mean observation period (years)	2.34	2.34
Observation period, min ; max, (years)	1.06 ; 5.06	1.06 ; 5.06
Total observation period (years)	11.72	11.72
Negative binomial analysis		
Annualised bleeding rate	20.28	20.28
95% CI	(12.09, 34.01)	(12.09, 34.01)
Poisson analysis		
Annualised bleeding rate	19.46	19.46
95% CI	(10.77, 35.15)	(10.77, 35.15)
Annualised bleeding rate, summary		
Mean (SD)	20.19 (13.18)	20.19 (13.18)
Median (IQR)	15.96 (17.75)	15.96 (17.75)
Min ; Max	6.62 ; 38.51	6.62 ; 38.51

CI: Confidence interval, SD: Standard deviation, IQR: Interquartile Range
A 95% CI for the annualised bleeding rate is estimated from a negative binomial model, with a sensitivity analysis using a Poisson model allowing for over-dispersion. If the number of patients per subgroup is less than 2, only the Poisson estimate of rate is provided.
* Number of patients with more than one exposure day reported, only these patients are included in the analysis.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_bleed_rate.sas/14200170_bl_rate_odage.txt

14.2.23 Annualised bleeding rate by haemophilia severity at inclusion - patients on on-demand regimen - full analysis set

	Severe	Moderately Severe	Total
Number of patients	3	1	5
N*	3	1	5
Number of patients with bleeds	3 (100.0)	1 (100.0)	5 (100.0)
Total number of bleeds	194	27	228
Mean bleeds per patient	64.67	27.00	45.60
Median bleeds per patient	56.00	27.00	37.00
Range of bleeds, min ; max	37 ; 101	27 ; 27	7 ; 101
Mean observation period (years)	2.99	1.69	2.34
Observation period, min ; max, (years)	1.28 ; 5.06	1.69 ; 1.69	1.06 ; 5.06
Total observation period (years)	8.97	1.69	11.72
Negative binomial analysis			
Annualised bleeding rate	25.93	NA	20.28
95% CI	(14.67, 45.84)	NA	(12.09, 34.01)
Poisson analysis			
Annualised bleeding rate	21.63	15.96	19.46
95% CI	(9.77, 47.87)	NA	(10.77, 35.15)
Annualised bleeding rate, summary			
Mean (SD)	26.13 (13.92)	15.96 (-)	20.19 (13.18)
Median (IQR)	28.82 (27.45)	15.96 (0.00)	15.96 (17.75)
Min ; Max	11.06 ; 38.51	15.96 ; 15.96	6.62 ; 38.51

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
CI: Confidence interval, SD: Standard deviation, IQR: Interquartile Range
A 95% CI for the annualised bleeding rate is estimated from a negative binomial model, with a sensitivity analysis using a Poisson model allowing for over-dispersion. If the number of patients per subgroup is less than 2, only the Poisson estimate of rate is provided.
* Number of patients with more than one exposure day reported, only these patients are included in the analysis.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_bleed_rate.sas/14200180_bl_rate_odfviii.txt

14.2.24 Annualised bleeding rate by age at inclusion - patients on prophylaxis regimen - traumatic bleeds - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	49	63
N*	14	48	62
Number of patients with bleeds	8 (57.1)	22 (45.8)	30 (48.4)
Total number of bleeds	24	47	71
Mean bleeds per patient	1.71	0.98	1.15
Median bleeds per patient	1.00	0.00	0.00
Range of bleeds, min ; max	0 ; 7	0 ; 8	0 ; 8
Mean observation period (years)	0.89	1.24	1.17
Observation period, min ; max, (years)	0.21 ; 1.71	0.21 ; 5.06	0.21 ; 5.06
Total observation period (years)	12.52	59.73	72.25
Negative binomial analysis			
Annualised bleeding rate	2.23	0.87	1.15
95% CI	(1.01, 4.95)	(0.55, 1.38)	(0.76, 1.73)
Poisson analysis			
Annualised bleeding rate	1.92	0.79	0.98
95% CI	(0.86, 4.28)	(0.50, 1.24)	(0.64, 1.51)
Annualised bleeding rate, summary			
Mean (SD)	2.24 (3.35)	0.86 (1.29)	1.17 (2.00)
Median (IQR)	0.65 (2.92)	0.00 (1.32)	0.00 (1.49)
Min ; Max	0.00 ; 9.25	0.00 ; 5.10	0.00 ; 9.25

CI: Confidence interval, SD: Standard deviation, IQR: Interquartile Range
A 95% CI for the annualised bleeding rate is estimated from a negative binomial model, with a sensitivity analysis using a Poisson model allowing for over-dispersion. If the number of patients per subgroup is less than 2, only the Poisson estimate of rate is provided.
* Number of patients with more than one exposure day reported with non-missing causality, only these patients are included inthe analysis.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_bleed_rate_cause.sas/14200181_bl_rate_page_traum.tx

14.2.25 Annualised bleeding rate by haemophilia severity at inclusion - patients on prophylaxis regimen - traumatic bleeds -full analysis set

	Severe	Moderately Severe	Total
Number of patients	55	8	63
N*	54	8	62
Number of patients with bleeds	28 (51.9)	2 (25.0)	30 (48.4)
Total number of bleeds	66	5	71
Mean bleeds per patient	1.22	0.63	1.15
Median bleeds per patient	1.00	0.00	0.00
Range of bleeds, min ; max	0 ; 8	0 ; 4	0 ; 8
Mean observation period (years)	1.20	0.96	1.17
Observation period, min ; max, (years)	0.21 ; 5.06	0.21 ; 1.97	0.21 ; 5.06
Total observation period (years)	64.61	7.64	72.25
Negative binomial analysis			
Annualised bleeding rate	1.21	0.72	1.15
95% CI	(0.79, 1.84)	(0.13, 4.13)	(0.76, 1.73)
Poisson analysis			
Annualised bleeding rate	1.02	0.65	0.98
95% CI	(0.65, 1.60)	(0.12, 3.57)	(0.64, 1.51)
Annualised bleeding rate, summary			
Mean (SD)	1.24 (2.05)	0.69 (1.73)	1.17 (2.00)
Median (IQR)	0.62 (1.62)	0.00 (0.30)	0.00 (1.49)
Min ; Max	0.00 ; 9.25	0.00 ; 4.95	0.00 ; 9.25

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
CI: Confidence interval, SD: Standard deviation, IQR: Interquartile Range
A 95% CI for the annualised bleeding rate is estimated from a negative binomial model, with a sensitivity analysis using a Poisson model allowing for over-dispersion. If the number of patients per subgroup is less than 2, only the Poisson estimate of rate is provided.
* Number of patients with more than one exposure day reported with non-missing causality, only these patients are included inthe analysis.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_bleed_rate_cause.sas/14200182_bl_rate_pfviii_traum.

14.2.26 Annualised bleeding rate by age at inclusion - patients on prophylaxis regimen - spontaneous bleeds - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	49	63
N*	14	48	62
Number of patients with bleeds	3 (21.4)	27 (56.3)	30 (48.4)
Total number of bleeds	8	153	161
Mean bleeds per patient	0.57	3.19	2.60
Median bleeds per patient	0.00	1.00	0.00
Range of bleeds, min ; max	0 ; 4	0 ; 31	0 ; 31
Mean observation period (years)	0.89	1.24	1.17
Observation period, min ; max, (years)	0.21 ; 1.71	0.21 ; 5.06	0.21 ; 5.06
Total observation period (years)	12.52	59.73	72.25
Negative binomial analysis			
Annualised bleeding rate	0.54	2.92	2.39
95% CI	(0.16, 1.85)	(1.80, 4.74)	(1.50, 3.81)
Poisson analysis			
Annualised bleeding rate	0.64	2.56	2.23
95% CI	(0.26, 1.59)	(1.62, 4.05)	(1.45, 3.43)
Annualised bleeding rate, summary			
Mean (SD)	0.46 (0.98)	2.99 (4.37)	2.42 (4.01)
Median (IQR)	0.00 (0.00)	1.10 (4.59)	0.00 (3.22)
Min ; Max	0.00 ; 3.22	0.00 ; 19.76	0.00 ; 19.76

CI: Confidence interval, SD: Standard deviation, IQR: Interquartile Range
A 95% CI for the annualised bleeding rate is estimated from a negative binomial model, with a sensitivity analysis using a Poisson model allowing for over-dispersion. If the number of patients per subgroup is less than 2, only the Poisson estimate of rate is provided.
* Number of patients with more than one exposure day reported with non-missing causality, only these patients are included inthe analysis.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_bleed_rate_cause.sas/14200183_bl_rate_page_spon.txt

14.2.27 Annualised bleeding rate by haemophilia severity at inclusion - patients on prophylaxis regimen - spontaneous bleeds -full analysis set

	Severe	Moderately Severe	Total
Number of patients	55	8	63
N*	54	8	62
Number of patients with bleeds	25 (46.3)	5 (62.5)	30 (48.4)
Total number of bleeds	143	18	161
Mean bleeds per patient	2.65	2.25	2.60
Median bleeds per patient	0.00	2.50	0.00
Range of bleeds, min ; max	0 ; 31	0 ; 5	0 ; 31
Mean observation period (years)	1.20	0.96	1.17
Observation period, min ; max, (years)	0.21 ; 5.06	0.21 ; 1.97	0.21 ; 5.06
Total observation period (years)	64.61	7.64	72.25
Negative binomial analysis			
Annualised bleeding rate	2.34	2.46	2.39
95% CI	(1.39, 3.96)	(1.24, 4.88)	(1.50, 3.81)
Poisson analysis			
Annualised bleeding rate	2.21	2.36	2.23
95% CI	(1.36, 3.60)	(1.23, 4.51)	(1.45, 3.43)
Annualised bleeding rate, summary			
Mean (SD)	2.34 (4.13)	3.00 (3.27)	2.42 (4.01)
Median (IQR)	0.00 (2.75)	2.46 (4.84)	0.00 (3.22)
Min ; Max	0.00 ; 19.76	0.00 ; 9.37	0.00 ; 19.76

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
CI: Confidence interval, SD: Standard deviation, IQR: Interquartile Range
A 95% CI for the annualised bleeding rate is estimated from a negative binomial model, with a sensitivity analysis using a Poisson model allowing for over-dispersion. If the number of patients per subgroup is less than 2, only the Poisson estimate of rate is provided.
* Number of patients with more than one exposure day reported with non-missing causality, only these patients are included inthe analysis.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_bleed_rate_cause.sas/14200184_bl_rate_pfviii_spon.t

14.2.28 Incidence rate of inhibitors by age at inclusion - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Incidence rate of FVIII inhibitors*, N (%)			
N	11	44	55
Incidence	0 (0.0)	0 (0.0)	0 (0.0)
97.5% UCL**	28.5	8.0	6.5
Poisson analysis			
Annualised inhibitor rate	0.000	0.000	0.000
95% CI***	-	-	-

UCL: Upper Confidence Limit
* N is number of patients with at least one inhibitor test after baseline. >=0.6 BU/mL for central laboratory analyses, or above the specific local laboratory reference range.
** 1-sided 97.5% upper confidence limit is based on an exact calculation for a binomial distribution
*** estimated from a Poisson model allowing for over-dispersion.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_inhib_inc.sas/14200190_incinh_age.txt

14.2.29 Incidence rate of inhibitors by haemophilia severity at inclusion - full analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Incidence rate of FVIII inhibitors*, N (%)			
N	48	6	55
Incidence	0 (0.0)	0 (0.0)	0 (0.0)
97.5% UCL**	7.4	45.9	6.5
Poisson analysis			
Annualised inhibitor rate	0.000	0.000	0.000
95% CI***	-	-	-

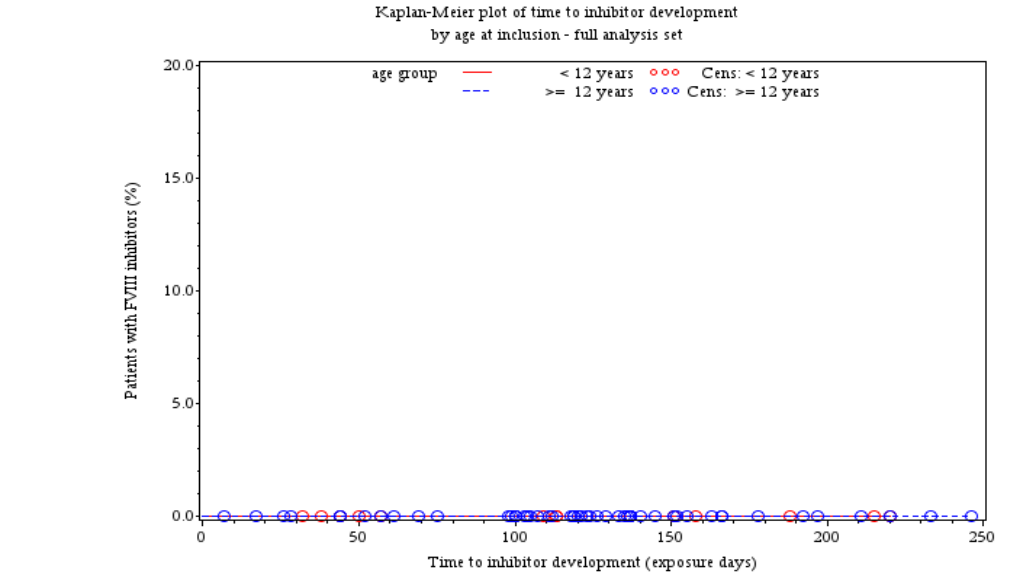
Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
UCL: Upper Confidence Limit
* N is number of patients with at least one inhibitor test after baseline. >=0.6 BU/mL for central laboratory analyses, or above the specific local laboratory reference range.
** 1-sided 97.5% upper confidence limit is based on an exact calculation for a binomial distribution
*** estimated from a Poisson model allowing for over-dispersion.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_inhib_inc.sas/14200200_incinh_fviii.txt

14.2.30 Incidence rate of inhibitors by treatment regimen - full analysis set

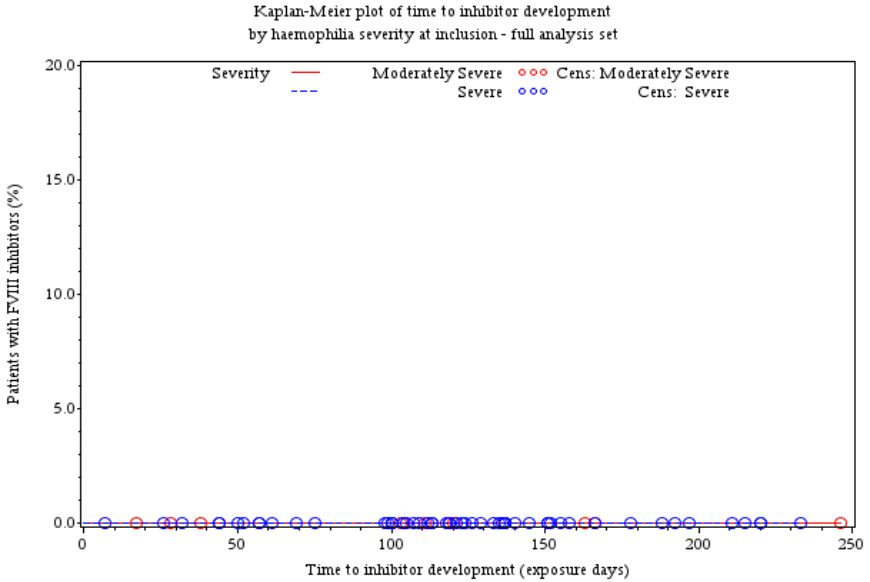
	Preventive regimen	On-demand regimen	Total
Number of patients	63	5	68
Incidence rate of FVIII inhibitors*, N (%)			
N	50	5	55
Incidence	0 (0.0)	0 (0.0)	0 (0.0)
97.5% UCL**	7.1	52.2	6.5
Poisson analysis			
Annualised inhibitor rate	0.000	0.000	0.000
95% CI***	-	-	-

UCL: Upper Confidence Limit
* N is number of patients with at least one inhibitor test after baseline. >=0.6 BU/mL for central laboratory analyses, or above the specific local laboratory reference range.
** 1-sided 97.5% upper confidence limit is based on an exact calculation for a binomial distribution
*** estimated from a Poisson model allowing for over-dispersion.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_inhib_inc.sas/14200210_incinh_reg.txt

14.2.31 Kaplan-Meier plot of time to inhibitor development by age at inclusion - full analysis set



14.2.32 Kaplan-Meier plot of time to inhibitor development by haemophilia severity at inclusion - full analysis set



Patients at risk

Moderately Severe	9	6	6	3	1	0
Severe	58	52	41	17	7	2

nn7008-3553/ctr_20201215_er - 15DEC2020 - f_1420_tti.sas/f_14200230_ttifviii

14.2.33 Exposure of FVIII during the study by age at inclusion - full analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Exposure days per patient*			
N	14	54	68
Mean (SD)	130.4 (88.1)	132.3 (102.4)	131.9 (99.0)
Median	113.0	122.0	120.5
Min ; Max	32.0 ; 337.0	7.0 ; 766.0	7.0 ; 766.0
Exposure days for prophylaxis per patient			
N	14	49	63
Mean (SD)	126.7 (88.3)	131.3 (104.7)	130.3 (100.6)
Median	104.0	121.0	121.0
Min ; Max	32.0 ; 337.0	4.0 ; 766.0	4.0 ; 766.0
Exposure days for treatment of bleed/surgery per patient			
N	8	39	47
Mean (SD)	6.8 (5.0)	18.3 (23.8)	16.3 (22.1)
Median	5.5	9.0	7.0
Min ; Max	2.0 ; 14.0	1.0 ; 116.0	1.0 ; 116.0

N: Number of patients, SD: Standard deviation.
* Includes all prophylaxis, treatment of bleed or surgery exposure days.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_expda.sas/14200240_expda_age.txt

14.2.34 Exposure of FVIII during the study by haemophilia severity at inclusion - full analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Exposure days per patient*			
N	58	9	68
Mean (SD)	136.8 (102.4)	110.1 (74.9)	131.9 (99.0)
Median	123.5	111.0	120.5
Min ; Max	7.0 ; 766.0	17.0 ; 245.0	7.0 ; 766.0
Exposure days for prophylaxis per patient			
N	55	8	63
Mean (SD)	133.7 (104.6)	107.1 (67.7)	130.3 (100.6)
Median	122.0	104.5	121.0
Min ; Max	4.0 ; 766.0	14.0 ; 240.0	4.0 ; 766.0
Exposure days for treatment of bleed/surgery per patient			
N	39	7	47
Mean (SD)	15.1 (22.9)	21.6 (19.6)	16.3 (22.1)
Median	7.0	16.0	7.0
Min ; Max	1.0 ; 116.0	1.0 ; 57.0	1.0 ; 116.0

N: Number of patients, SD: Standard deviation.
* Includes all prophylaxis, treatment of bleed or surgery exposure days.
Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column
to represent the full analysis set.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1420_expda.sas/14200250_expda_fviii.txt

14.3 Safety data

14.3.1 Displays of adverse events

14.3.1.1 Overview of adverse reactions by age at inclusion - safety analysis set

	Baseline age <12 years N (%) E [R]	Baseline age >= 12 years N (%) E [R]	Total N (%) E [R]
Number of patients	14	54	68
Total time in study (years)	12.51	75.27	87.78
Total number of exposure days	1825	7142	8967
All adverse reactions	-	1 (1.9) 1 [0.01]	1 (1.5) 1 [0.01]
Serious adverse reactions	-	1 (1.9) 1 [0.01]	1 (1.5) 1 [0.01]
Adverse reactions by severity			
Moderate	-	1 (1.9) 1 [0.01]	1 (1.5) 1 [0.01]
Adverse reactions by relationship			
Probably or possibly related	-	1 (1.9) 1 [0.01]	1 (1.5) 1 [0.01]
Adverse reactions			
Leading to withdrawal	-	-	-

All adverse reactions in this table are treatment emergent.
N: Number of patients with adverse reactions, %: Percentage of patients with adverse reactions,
E: Number of adverse reactions
[R]: Number of adverse reactions per patient years of exposure (E/total time in study phase)
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1431_teae_ov.sas/14310010_adr_ovage.txt

14.3.1.2 Overview of adverse reactions by haemophilia severity at inclusion - safety analysis set

	Severe N (%) E [R]	Moderately Severe N (%) E [R]	Total N (%) E [R]
Number of patients	58	9	68
Total time in study (years)	76.30	10.42	87.78
Total number of exposure days	7932	991	8967
All adverse reactions	1 (1.7) 1 [0.01]	-	1 (1.5) 1 [0.01]
Serious adverse reactions	1 (1.7) 1 [0.01]	-	1 (1.5) 1 [0.01]
Adverse reactions by severity Moderate	1 (1.7) 1 [0.01]	-	1 (1.5) 1 [0.01]
Adverse reactions by relationship Probably or possibly related	1 (1.7) 1 [0.01]	-	1 (1.5) 1 [0.01]
Adverse reactions Leading to withdrawal	-	-	-

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
All adverse reactions in this table are treatment emergent.
N: Number of patients with adverse reactions, %: Percentage of patients with adverse reactions,
E: Number of adverse reactions
[R]: Number of adverse reactions per patient years of exposure (E/total time in study phase)

nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1431_teae_ov.sas/14310020_adr_ovfviii.txt

14.3.1.3 Overview of adverse reactions by treatment regimen - safety analysis set

	Preventive regimen N (%) E [R]	On-Demand regimen N (%) E [R]	Total N (%) E [R]
Number of patients	63	5	68
Total time in study (years)	76.07	11.71	87.78
Total number of exposure days	8655	312	8967
All adverse reactions	1 (1.6) 1 [0.01]	-	1 (1.5) 1 [0.01]
Serious adverse reactions	1 (1.6) 1 [0.01]	-	1 (1.5) 1 [0.01]
Adverse reactions by severity			
Moderate	1 (1.6) 1 [0.01]	-	1 (1.5) 1 [0.01]
Adverse reactions by relationship			
Probably or possibly related	1 (1.6) 1 [0.01]	-	1 (1.5) 1 [0.01]
Adverse reactions			
Leading to withdrawal	-	-	-

All adverse reactions in this table are treatment emergent.
N: Number of patients with adverse reactions, %: Percentage of patients with adverse reactions,
E: Number of adverse reactions
[R]: Number of adverse reactions per patient years of exposure (E/total time in study phase)

nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1431_teae_ov.sas/14310030_adr_ovreg.txt

14.3.1.4 Adverse reactions by system organ class, preferred term and age at inclusion - safety analysis set

	Baseline age <12 years N (%) E [R]	Baseline age >= 12 years N (%) E [R]	Total N (%) E [R]
Number of patients	14	54	68
Total time in study (years)	12.51	75.27	87.78
Total number of exposure days	1825	7142	8967
All adverse reactions	-	1 (1.9) 1 [0.01]	1 (1.5) 1 [0.01]
Cardiac disorders	-	1 (1.9) 1 [0.01]	1 (1.5) 1 [0.01]
Angina pectoris	-	1 (1.9) 1 [0.01]	1 (1.5) 1 [0.01]

N: Number of patients with adverse reactions, %: Percentage of patients with adverse reactions,
E: Number of adverse reactions.
[R]: Number of adverse reactions per patient years of exposure (E/total time in study).
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1431_teae.sas/14310040_adrage.txt

14.3.1.5 Adverse reactions by system organ class, preferred term and haemophilia severity at inclusion - safety analysis set

	Severe N (%) E [R]	Moderately Severe N (%) E [R]	Total N (%) E [R]
Number of patients	58	9	68
Total time in study (years)	76.30	10.42	87.78
Total number of exposure days	7932	991	8967
All adverse reactions	1 (1.7) 1 [0.01]	-	1 (1.5) 1 [0.01]
Cardiac disorders	1 (1.7) 1 [0.01]	-	1 (1.5) 1 [0.01]
Angina pectoris	1 (1.7) 1 [0.01]	-	1 (1.5) 1 [0.01]

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
N: Number of patients with adverse reactions, %: Percentage of patients with adverse reactions,
E: Number of adverse reactions.
[R]: Number of adverse reactions per patient years of exposure (E/total time in study).
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1431_teae.sas/14310050_adrfviii.txt

14.3.1.6 Severe adverse reactions by system organ class, preferred term and age at inclusion - safety analysis set

There is no data to display

nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1431_teae.sas/14310060_adr_sevage.txt

14.3.1.7 Moderate adverse reactions by system organ class, preferred term and age at inclusion - safety analysis set

	Baseline age <12 years N (%) E [R]	Baseline age >= 12 years N (%) E [R]	Total N (%) E [R]
Number of patients	14	54	68
Total time in study (years)	12.51	75.27	87.78
Total number of exposure days	1825	7142	8967
All adverse reactions	-	1 (1.9) 1 [0.01]	1 (1.5) 1 [0.01]
Cardiac disorders	-	1 (1.9) 1 [0.01]	1 (1.5) 1 [0.01]
Angina pectoris	-	1 (1.9) 1 [0.01]	1 (1.5) 1 [0.01]

N: Number of patients with adverse reactions, %: Percentage of patients with adverse reactions,
E: Number of adverse reactions.
[R]: Number of adverse reactions per patient years of exposure (E/total time in study).

nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1431_teae.sas/14310070_adr_modage.txt

14.3.1.8 Mild adverse reactions by system organ class, preferred term and age at inclusion - safety analysis set

There is no data to display

nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1431_teae.sas/14310080_adr_milage.txt

14.3.1.9 Severe adverse reactions by system organ class, preferred term and haemophilia severity at inclusion - safety analysis set

There is no data to display

nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1431_teae.sas/14310090_adr_sevfviii.txt

14.3.1.10 Moderate adverse reactions by system organ class, preferred term and haemophilia severity at inclusion - safety analysis set

	Severe N (%) E [R]	Moderately Severe N (%) E [R]	Total N (%) E [R]
Number of patients	58	9	68
Total time in study (years)	76.30	10.42	87.78
Total number of exposure days	7932	991	8967
All adverse reactions	1 (1.7) 1 [0.01]	-	1 (1.5) 1 [0.01]
Cardiac disorders	1 (1.7) 1 [0.01]	-	1 (1.5) 1 [0.01]
Angina pectoris	1 (1.7) 1 [0.01]	-	1 (1.5) 1 [0.01]

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
N: Number of patients with adverse reactions, %: Percentage of patients with adverse reactions,
E: Number of adverse reactions.
[R]: Number of adverse reactions per patient years of exposure (E/total time in study).

nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1431_teae.sas/14310100_adr_modfviii.txt

14.3.1.11 Mild adverse reactions by system organ class, preferred term and haemophilia severity at inclusion - safety analysis set

There is no data to display

nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1431_teae.sas/14310110_adr_milfviii.txt

14.3.1.12 Serious adverse reactions by system organ class, preferred term and age at inclusion - safety analysis set

	Baseline age <12 years N (%) E [R]	Baseline age >= 12 years N (%) E [R]	Total N (%) E [R]
Number of patients	14	54	68
Total time in study (years)	12.51	75.27	87.78
Total number of exposure days	1825	7142	8967
All adverse reactions	-	1 (1.9) 1 [0.01]	1 (1.5) 1 [0.01]
Cardiac disorders	-	1 (1.9) 1 [0.01]	1 (1.5) 1 [0.01]
Angina pectoris	-	1 (1.9) 1 [0.01]	1 (1.5) 1 [0.01]

N: Number of patients with adverse reactions, %: Percentage of patients with adverse reactions,
E: Number of adverse reactions.
[R]: Number of adverse reactions per patient years of exposure (E/total time in study).
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1431_teae.sas/14310120_teae_serage.txt

14.3.1.13 Serious adverse reactions by system organ class, preferred term and haemophilia severity at inclusion - safety analysis set

	Severe N (%) E [R]	Moderately Severe N (%) E [R]	Total N (%) E [R]
Number of patients	58	9	68
Total time in study (years)	76.30	10.42	87.78
Total number of exposure days	7932	991	8967
All adverse reactions	1 (1.7) 1 [0.01]	-	1 (1.5) 1 [0.01]
Cardiac disorders	1 (1.7) 1 [0.01]	-	1 (1.5) 1 [0.01]
Angina pectoris	1 (1.7) 1 [0.01]	-	1 (1.5) 1 [0.01]

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
N: Number of patients with adverse reactions, %: Percentage of patients with adverse reactions,
E: Number of adverse reactions.
[R]: Number of adverse reactions per patient years of exposure (E/total time in study).
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1431_teae.sas/14310130_teae_serfviii.txt

14.3.1.14 Adverse events of special interest by age at inclusion - safety analysis set

```
There is no data to display
```


14.3.1.15 Adverse events of special interest by haemophilia severity at inclusion - safety analysis set

```
There is no data to display
```

14.3.2 Listings of deaths, other serious and significant adverse events

14.3.2.1 Serious adverse reactions by patient - safety analysis set

Patient ID/ Age group/ Severity	AE no	System organ class/ Preferred term/ Investigator's description	Days since first/ latest dose	Age (yrs)/ ED at onset	Onset/ Resolution date	Duration (days)	Serious/ Life*/ AESI (Y/N)	Severity/ Relation-ship	Action/ Outcome
[redacted]									

ED is the number of exposure days before onset of event.
AE: Adverse event, ADR: Adverse drug reactions, AESI: Adverse event of special interest.
* Life: Indicated whether a serious AE is life-threatening or not.

14.3.2.2 Adverse reactions leading to withdrawal by patient - safety analysis set

```
There is no data to display
```


14.3.2.3 Adverse reactions leading to death by patient - safety analysis set

```
There is no data to display
```

14.3.3 Narratives of deaths, other serious and selected significant adverse events

Narrative cover page

This section contains narratives on serious adverse events. There were no cases of deaths, adverse events of special interest, withdrawals due to adverse reaction reported in this study.

Narratives on other serious adverse events, were extracted from the safety database (Global Safety, Novo Nordisk) on 25-May-2020.

Narratives are bookmarked by category:

- serious adverse events

If a case belongs to multiple categories, the case is bookmarked under all the categories to which it belongs.

Narrative overview table

Data cut-off: 25-May-2020

Subject ID	Case number	Reason(s) for narrative	Preferred term	Assigned treatment group	Actual treatment (if different from assigned)
[redacted]					

Report #: **NN7008-3553 SAE** Date: 26-May-2020 12:47:52

Period: 01-Jan-1900 Through 25-May-2020

Ingredient: **turoctocog alfa**

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term] Ser/UL/Causal	Patient Outcome
[redacted]								

* SUSAR Event.

Report #: **NN7008-3553 SAE** Date: 26-May-2020 12:47:52

Period: 01-Jan-1900 Through 25-May-2020

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term] Ser/UL/Causal	Patient Outcome
[redacted]								

Total number of case entries printed in the Initial section: 1
Total number of cases printed in the Initial section: 1
Total number of case entries printed in the Medically Confirmed section: 1
Total number of cases printed in the Medically Confirmed section: 1
Total number of case entries printed in the Serious or Unlisted section: 1
Total number of cases printed in the Serious or Unlisted section: 1
Total number of case entries printed: 1
Total number of cases printed: 1

* SUSAR Event.

Report #: **NN7008-3553 SAE** Date: 26-May-2020 12:47:52

Period: 01-Jan-1900 Through 25-May-2020

Index of Cases in Report

[redacted]

Report #: **NN7008-3553 SUSAR** Date: 26-May-2020 12:50:54

Period: 01-Jan-1900 Through 25-May-2020

Ingredient: **turoctocog alfa**

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term] Ser/UL/Causal	Patient Outcome
Initial (**1**)								
Medically Confirmed (**1**)								
Serious or Unlisted (**1**)								
Event System Organ Class: Cardiac disorders (**1**)								
Event Preferred Term: Angina pectoris (**1**)								
[redacted]								

* SUSAR Event.

Report #: **NN7008-3553 SUSAR** Date: 26-May-2020 12:50:54

Period: 01-Jan-1900 Through 25-May-2020

Case Number	Country Source	Age Sex	Product Name / Form Daily Dose [Dose Frequency]	Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term] Ser/UL/Causal	Patient Outcome
[redacted]								

Total number of case entries printed in the Initial section: 1
Total number of cases printed in the Initial section: 1
Total number of case entries printed in the Medically Confirmed section: 1
Total number of cases printed in the Medically Confirmed section: 1
Total number of case entries printed in the Serious or Unlisted section: 1
Total number of cases printed in the Serious or Unlisted section: 1
Total number of case entries printed: 1
Total number of cases printed: 1

* SUSAR Event.

Report #: **NN7008-3553 SUSAR** Date: 26-May-2020 12:50:54

Period: 01-Jan-1900 Through 25-May-2020

Index of Cases in Report

[redacted]

Report #:

NN7008-3553 Fatal Cases

Date: 26-May-2020 12:39:13

Period: 01-Jan-1900 Through 25-May-2020

Ingredient: **turoctocog alfa**

Case Number	Country Source	Age Sex	Daily Dose [Dose Frequency]	Form / Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term] Ser/UL/Causal	Patient Outcome

No Data Found

Report #: **NN7008-3553 MESI/AESI** Date: 26-May-2020 12:41:58

Period: 01-Jan-1900 Through 25-May-2020

Ingredient: **turoctocog alfa**

Case Number	Country Source	Age Sex	Daily Dose [Dose Frequency]	Form / Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term] Ser/UL/Causal	Patient Outcome

No Data Found

Report #: **NN7008-3553 Unblinded** Date: 26-May-2020 12:51:33

Period: 01-Jan-1900 Through 25-May-2020

Ingredient: **turoctocog alfa**

Case Number	Country Source	Age Sex	Daily Dose [Dose Frequency]	Form / Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term] Ser/UL/Causal	Patient Outcome

No Data Found

Report #: **NN7008-3553 Pregnancy** Date: 26-May-2020 12:45:03

Period: 01-Jan-1900 Through 25-May-2020

Ingredient: **turoctocog alfa**

Case Number	Country Source	Age Sex	Daily Dose [Dose Frequency]	Form / Route	Dates of Treatment or Treatment Duration	Event Onset Date or Time to Onset	Event Verbatim [Preferred Term] Ser/UL/Causal	Patient Outcome

No Data Found

14.3.4 Abnormal laboratory value listings (by subject)

14.3.4.1 Listing of laboratory reference ranges

Category	Parameter	Substance	LabID	Age range	Age range unit	Reference range lower limit (char)	Reference range upper limit (char)	Analysis unit
Biochemistry	Sodium		[redacted]	0 - 120	YEARS - YEARS	135	150	mmol/L
				0 - 99	YEARS - YEARS	135	145	mmol/L
				18 - 99	YEARS - YEARS	136	146	mmol/L
				18 - 99	YEARS - YEARS	134	146	mmol/L
				18 - 99	YEARS - YEARS	135	145	mmol/L
				0 - 99	YEARS - YEARS	136	145	mmol/L
				0 - 99	YEARS - YEARS	136	145	mmol/L
				0 - 99	YEARS - YEARS	136	145	mmol/L
				0 - 99	YEARS - YEARS	133	146	mmol/L
				0 - 99	YEARS - YEARS	135	145	mmol/L
				6 - 7	YEARS - YEARS	135	145	mmol/L
				18 - 99	YEARS - YEARS	135	145	mmol/L
				18 - 99	YEARS - YEARS	136	143	mmol/L
	Potassium			0 - 120	YEARS - YEARS	3.5	5.3	mmol/L
				0 - 99	YEARS - YEARS	3.6	4.8	mmol/L
				18 - 99	YEARS - YEARS	3.5	5.1	mmol/L
				18 - 99	YEARS - YEARS	3.3	5.4	mmol/L
				18 - 99	YEARS - YEARS	3.5	5.0	mmol/L
				0 - 99	YEARS - YEARS	3.5	5.1	mmol/L
				0 - 99	YEARS - YEARS	3.3	5.1	mmol/L
				0 - 99	YEARS - YEARS	3.5	5.1	mmol/L
				0 - 99	YEARS - YEARS	3.5	5.3	mmol/L
				18 - 99	YEARS - YEARS	0.8	1.5	mmol/L
				6 - 7	YEARS - YEARS	3.8	5.5	mmol/L
				18 - 99	YEARS - YEARS	3.8	5.5	mmol/L
				18 - 99	YEARS - YEARS	3.8	4.9	mmol/L
	Serum Chloride			0 - 120	YEARS - YEARS	95	110	mmol/L
				0 - 99	YEARS - YEARS	95	105	mmol/L
				18 - 99	YEARS - YEARS	97	108	mmol/L
				0 - 99	YEARS - YEARS	98	107	mmol/L
				0 - 99	YEARS - YEARS	98	107	mmol/L
				0 - 99	YEARS - YEARS	99	111	mmol/L
				0 - 99	YEARS - YEARS	93	107	mmol/L
				6 - 7	YEARS - YEARS	95	107	mmol/L
				18 - 99	YEARS - YEARS	95	105	mmol/L

Listing of laboratory reference ranges

Continued...

Category	Parameter	Substance	LabID	Age range	Age range unit	Reference range lower limit (char)	Reference range upper limit (char)	Analysis unit
Biochemistry	Calcium		[redacted]	0 - 120	YEARS - YEARS	2.15	2.65	mmol/L
				0 - 99	YEARS - YEARS	2.20	2.60	mmol/L
				18 - 99	YEARS - YEARS	2.20	2.70	mmol/L
				0 - 99	YEARS - YEARS	2.12	2.52	mmol/L
				0 - 99	YEARS - YEARS	2.10	2.54	mmol/L
				0 - 99	YEARS - YEARS	2.10	2.60	mmol/L
				0 - 99	YEARS - YEARS	2.20	2.55	mmol/L
				6 - 7	YEARS - YEARS	2.10	2.60	mmol/L
				18 - 99	YEARS - YEARS	2.10	2.60	mmol/L
	Total Cholesterol			0 - 99	YEARS - YEARS	3.20	5.65	mmol/L
				18 - 99	YEARS - YEARS		<250	mmol/L
				18 - 99	YEARS - YEARS	3.11	5.70	mmol/L
				0 - 99	YEARS - YEARS	0.00	5.18	mmol/L
				0 - 99	YEARS - YEARS	0.00	5.00	mmol/L
					YEARS - YEARS	0.00	5.00	
				18 - 99	YEARS - YEARS	0.00	5.20	mmol/L
				0 - 99	YEARS - YEARS	3.60	5.70	mmol/L
				18 - 99	YEARS - YEARS	3.63	5.18	mmol/L
Biochemistry	Creatinine			15 - 120	YEARS - YEARS	59	103	umol/L
				0 - 99	YEARS - YEARS	50	110	umol/L
				0 - 99	YEARS - YEARS	64	104	umol/L
				9 - 15	YEARS - YEARS	34	77	umol/L
				15 - 120	YEARS - YEARS	62	106	umol/L
				18 - 99	YEARS - YEARS	74	111	umol/L
				18 - 99	YEARS - YEARS	62	115	umol/L
				0 - 99	YEARS - YEARS	62	115	umol/L
				0 - 99	YEARS - YEARS	59	103	umol/L
				18 - 65	YEARS - YEARS	56	101	umol/L
				0 - 99	YEARS - YEARS	59	103	umol/L
				0 - 99	YEARS - YEARS	44	106	umol/L
				15 - 99	YEARS - YEARS	64	104	umol/L
					YEARS - YEARS	64	104	
				18 - 99	YEARS - YEARS	62	106	umol/L
				0 - 99	YEARS - YEARS	35	116	umol/L
				18 - 99	YEARS - YEARS	44	97	umol/L

Listing of laboratory reference ranges

Continued...

Category	Parameter	Substance	LabID	Age range	Age range unit	Reference range lower limit (char)	Reference range upper limit (char)	Analysis unit
Biochemistry	Creatinine		[redacted]	18 - 99	YEARS - YEARS	62	106	umol/L
				18 - 99	YEARS - YEARS	62	106	umol/L
	Urea			0 - 120	YEARS - YEARS	0.6	1.2	mmol/L
				0 - 99	YEARS - YEARS	2.5	6.6	mmol/L
				0 - 99	YEARS - YEARS	2.5	7.0	mmol/L
				14 - 18	YEARS - YEARS	2.9	7.5	mmol/L
				18 - 99	YEARS - YEARS	2.8	7.2	mmol/L
				18 - 99	YEARS - YEARS	1.7	8.3	mmol/L
				0 - 99	YEARS - YEARS	1.7	8.3	mmol/L
				4 - 13	YEARS - YEARS	2.5	6.0	mmol/L
				0 - 99	YEARS - YEARS	4.2	10.7	mmol/L
				0 - 99	YEARS - YEARS	1.7	8.3	mmol/L
				0 - 99	YEARS - YEARS	1.7	8.3	mmol/L
				18 - 99	YEARS - YEARS	3.6	7.2	mmol/L
				0 - 99	YEARS - YEARS	2.5	8.0	mmol/L
				6 - 7	YEARS - YEARS	2.8	6.7	mmol/L
				18 - 99	YEARS - YEARS	2.8	7.5	mmol/L
				18 - 99	YEARS - YEARS	2.8	8.2	mmol/L
Biochemistry	Albumin			0 - 99	YEARS - YEARS	35	55	g/L
				18 - 99	YEARS - YEARS	56	66	%
				18 - 99	YEARS - YEARS	34	48	g/L
				0 - 99	YEARS - YEARS	35	52	g/L
				0 - 99	YEARS - YEARS	34	48	g/L
				0 - 99	YEARS - YEARS	56	66	%
				3 - 99	YEARS - YEARS	35	50	g/L
				0 - 99	YEARS - YEARS	35	52	g/L
				0 - 99	YEARS - YEARS	35	50	g/L
				18 - 99	YEARS - YEARS	32	55	g/L
				18 - 99	YEARS - YEARS	40	49	g/L
				18 - 99	YEARS - YEARS	35	50	g/L
	Total bilirubin			0 - 120	YEARS - YEARS	2	21	umol/L
				0 - 99	YEARS - YEARS	0	17	umol/L
				0 - 99	YEARS - YEARS	2	21	umol/L
				15 - 18	YEARS - YEARS	0	12	umol/L

Listing of laboratory reference ranges

Continued...

Category	Parameter	Substance	LabID	Age range	Age range unit	Reference range lower limit (char)	Reference range upper limit (char)	Analysis unit
Biochemistry	Total bilirubin		[redacted]	18 - 99	YEARS - YEARS		<1.2	umol/L
				0 - 99	YEARS - YEARS	3	21	umol/L
				0 - 99	YEARS - YEARS	3	17	umol/L
				0 - 99	YEARS - YEARS	0	17	umol/L
				0 - 99	YEARS - YEARS		<21	umol/L
				18 - 99	YEARS - YEARS	5	21	umol/L
	Alkaline phosphatase			0 - 120	YEARS - YEARS	30	120	IU/L
				3 - 15	YEARS - YEARS	110	390	IU/L
				15 - 17	YEARS - YEARS	82	331	IU/L
				18 - 99	YEARS - YEARS	40	130	IU/L
				18 - 99	YEARS - YEARS	40	129	IU/L
				2 - 10	YEARS - YEARS	142	335	IU/L
				0 - 99	YEARS - YEARS	50	130	IU/L
				0 - 99	YEARS - YEARS	40	129	IU/L
				0 - 99	YEARS - YEARS	40	129	IU/L
				19 - 99	YEARS - YEARS	0	120	IU/L
				18 - 99	YEARS - YEARS	40	115	IU/L
				18 - 99	YEARS - YEARS	0	270	IU/L
				18 - 99	YEARS - YEARS	40	129	IU/L
	ALAT			0 - 120	YEARS - YEARS	10	45	IU/L
				0 - 99	YEARS - YEARS	5	45	IU/L
				0 - 99	YEARS - YEARS	9	59	IU/L
				13 - 18	YEARS - YEARS	0	45	IU/L
				18 - 99	YEARS - YEARS		<50	IU/L
				18 - 99	YEARS - YEARS	10	50	IU/L
				0 - 99	YEARS - YEARS	0	50	IU/L
				2 - 12	YEARS - YEARS	7	44	IU/L
				0 - 99	YEARS - YEARS	12	65	IU/L
				0 - 99	YEARS - YEARS	0	41	IU/L
				0 - 99	YEARS - YEARS	10	41	IU/L
				0 - 99	YEARS - YEARS	0	45	IU/L
					YEARS - YEARS	0	45	
				0 - 99	YEARS - YEARS	0	40	IU/L
				0 - 99	YEARS - YEARS	0	49	IU/L
				18 - 99	YEARS - YEARS		<50	IU/L

Listing of laboratory reference ranges

Continued...

Category	Parameter	Substance	LabID	Age range	Age range unit	Reference range lower limit (char)	Reference range upper limit (char)	Analysis unit
Biochemistry	ALAT		[redacted]	18 - 99	YEARS - YEARS	0	40	IU/L
	Serum GGT			16 - 120	YEARS - YEARS	12	55	IU/L
				0 - 99	YEARS - YEARS	9	40	IU/L
				13 - 18	YEARS - YEARS	0	29	IU/L
				18 - 99	YEARS - YEARS		<60	IU/L
				18 - 99	YEARS - YEARS	10	66	IU/L
				0 - 99	YEARS - YEARS	0	55	IU/L
				0 - 99	YEARS - YEARS	5	85	IU/L
				0 - 99	YEARS - YEARS	8	61	IU/L
				0 - 99	YEARS - YEARS	8	61	IU/L
				1 - 99	YEARS - YEARS	0	55	IU/L
					YEARS - YEARS	0	55	
				0 - 99	YEARS - YEARS	7	50	IU/L
				18 - 99	YEARS - YEARS	0	50	IU/L
				6 - 7	YEARS - YEARS	4	22	IU/L
				18 - 99	YEARS - YEARS		<50	IU/L
				18 - 99	YEARS - YEARS	8	61	IU/L
	Aspartate aminotransferase			0 - 120	YEARS - YEARS	10	35	IU/L
				0 - 99	YEARS - YEARS	5	35	IU/L
				0 - 99	YEARS - YEARS	11	34	IU/L
				13 - 18	YEARS - YEARS	0	46	IU/L
				18 - 99	YEARS - YEARS		<50	IU/L
				18 - 99	YEARS - YEARS	10	50	IU/L
				0 - 99	YEARS - YEARS	0	50	IU/L
				0 - 99	YEARS - YEARS	15	37	IU/L
				0 - 99	YEARS - YEARS	0	37	IU/L
				0 - 99	YEARS - YEARS	10	37	IU/L
				3 - 99	YEARS - YEARS	0	35	IU/L
				0 - 99	YEARS - YEARS	0	40	IU/L
				0 - 99	YEARS - YEARS	0	46	IU/L
				18 - 99	YEARS - YEARS		<50	IU/L
				18 - 99	YEARS - YEARS	15	40	IU/L
Biochemistry	Total proteins			0 - 120	YEARS - YEARS	65	85	g/L
				0 - 99	YEARS - YEARS	60	80	g/L

Listing of laboratory reference ranges

Continued...

Category	Parameter	Substance	LabID	Age range	Age range unit	Reference range lower limit (char)	Reference range upper limit (char)	Analysis unit
Biochemistry	Total proteins		[redacted]	2 - 120	YEARS - YEARS	65	80	g/L
				18 - 99	YEARS - YEARS	66	83	g/L
				18 - 99	YEARS - YEARS	66	87	g/L
				3 - 18	YEARS - YEARS	60	80	g/L
				0 - 99	YEARS - YEARS	64	82	g/L
				0 - 99	YEARS - YEARS	66	87	g/L
				0 - 99	YEARS - YEARS	59	84	g/L
				0 - 99	YEARS - YEARS	60	80	g/L
				0 - 99	YEARS - YEARS	64	83	g/L
				18 - 99	YEARS - YEARS	65	80	g/L
				18 - 99	YEARS - YEARS	60	80	g/L
Haematology	Haemoglobin			16 - 120	YEARS - YEARS	8	11	mmol/L
				9 - 17	YEARS - YEARS	8	10	mmol/L
				0 - 99	YEARS - YEARS	8	11	mmol/L
				13 - 16	YEARS - YEARS	7	10	mmol/L
				18 - 99	YEARS - YEARS	8	11	mmol/L
				18 - 99	YEARS - YEARS	9	11	mmol/L
				6 - 12	YEARS - YEARS	7	9	mmol/L
				18 - 99	YEARS - YEARS	8	11	mmol/L
				0 - 99	YEARS - YEARS	9	11	mmol/L
				0 - 15	YEARS - YEARS	8	10	mmol/L
				0 - 99	YEARS - YEARS	9	11	mmol/L
				0 - 99	YEARS - YEARS	7	11	mmol/L
				0 - 99	YEARS - YEARS	7	11	mmol/L
				1 - 12	YEARS - YEARS	7	9	mmol/L
				12 - 99	YEARS - YEARS	9	11	mmol/L
					YEARS - YEARS	9	11	
				18 - 99	YEARS - YEARS	8	10	mmol/L
				18 - 99	YEARS - YEARS	9	11	mmol/L
				18 - 99	YEARS - YEARS	7	10	mmol/L
				6 - 7	YEARS - YEARS	7	8	mmol/L
				6 - 99	YEARS - YEARS	8	11	mmol/L
				18 - 99	YEARS - YEARS	8	11	mmol/L
				18 - 99	YEARS - YEARS	8	11	mmol/L
					YEARS - YEARS	8	11	

Listing of laboratory reference ranges

Continued...

Category	Parameter	Substance	LabID	Age range	Age range unit	Reference range lower limit (char)	Reference range upper limit (char)	Analysis unit
Haematology	White cell count		[redacted]	16 - 120	YEARS - YEARS	4.0	11.0	10^9/L
				0 - 99	YEARS - YEARS	4.1	10.5	10^9/L
				18 - 99	YEARS - YEARS	3.5	9.8	10^9/L
				0 - 99	YEARS - YEARS	4.0	10.0	10^9/L
				0 - 99	YEARS - YEARS	4.0	10.0	10^9/L
				16 - 99	YEARS - YEARS	4.0	10.0	10^9/L
					YEARS - YEARS	4.0	10.0	
				12 - 99	YEARS - YEARS	4.5	10.8	10^9/L
				0 - 99	YEARS - YEARS	4.0	10.0	10^9/L
				18 - 99	YEARS - YEARS	3.9	8.8	10^9/L
				6 - 7	YEARS - YEARS	4.3	11.0	10^9/L
				6 - 99	YEARS - YEARS	4.0	10.0	10^9/L
	Red cell count			16 - 120	YEARS - YEARS	4.5	5.9	10^12/L
				9 - 17	YEARS - YEARS	4.2	5.4	10^12/L
				0 - 99	YEARS - YEARS	4.5	6.5	10^12/L
				18 - 99	YEARS - YEARS	4.5	5.9	10^12/L
				6 - 12	YEARS - YEARS	4.5	5.5	10^6/uL
				18 - 99	YEARS - YEARS	4.2	5.8	10^12/L
				0 - 99	YEARS - YEARS	4.5	5.9	10^12/L
				0 - 15	YEARS - YEARS	4.1	4.6	10^6/uL
				0 - 99	YEARS - YEARS	4.5	6.1	10^12/L
				0 - 99	YEARS - YEARS	3.8	5.0	10^6/uL
				0 - 99	YEARS - YEARS	3.7	5.1	10^6/uL
				0 - 99	YEARS - YEARS	4.2	5.5	10^12/L
				18 - 99	YEARS - YEARS	4.7	6.0	10^12/L
				18 - 99	YEARS - YEARS	4.5	5.5	10^6/uL
				18 - 99	YEARS - YEARS	4.2	5.5	10^12/L
				6 - 7	YEARS - YEARS	4.0	5.0	10^12/L
				6 - 99	YEARS - YEARS	4.5	5.5	10^12/L
				18 - 99	YEARS - YEARS	4.2	5.7	10^12/L
				18 - 99	YEARS - YEARS	4.6	6.2	10^12/L
	MCV			16 - 120	YEARS - YEARS	80	100	fL
				9 - 99	YEARS - YEARS	78	100	fL
				0 - 99	YEARS - YEARS	80	100	fL
				12 - 15	YEARS - YEARS	77	95	fL

Listing of laboratory reference ranges

Continued...

Category	Parameter	Substance	LabID	Age range	Age range unit	Reference range lower limit (char)	Reference range upper limit (char)	Analysis unit
Haematology	MCV		[redacted]	13 - 16	YEARS - YEARS	78	93	fL
				18 - 99	YEARS - YEARS	80	96	fL
				18 - 99	YEARS - YEARS	80	96	fL
				6 - 12	YEARS - YEARS	71	84	fL
				18 - 99	YEARS - YEARS	90	99	fL
				0 - 99	YEARS - YEARS	77	100	fL
				0 - 99	YEARS - YEARS	79	92	fL
				0 - 99	YEARS - YEARS	81	94	fL
				0 - 99	YEARS - YEARS	80	99	fL
				0 - 99	YEARS - YEARS	80	99	fL
				12 - 99	YEARS - YEARS	80	97	fL
				18 - 99	YEARS - YEARS	80	99	fL
				0 - 99	YEARS - YEARS	80	96	fL
				18 - 99	YEARS - YEARS	80	94	fL
				6 - 7	YEARS - YEARS	74	86	fL
				6 - 99	YEARS - YEARS	83	101	fL
				18 - 99	YEARS - YEARS	80	100	fL
				18 - 99	YEARS - YEARS	80	96	fL
	MCH			9 - 17	YEARS - YEARS	1.6	2.0	fmol
				0 - 99	YEARS - YEARS	1.7	2.0	fmol
				4 - 15	YEARS - YEARS	1.4	2.2	fmol
				13 - 16	YEARS - YEARS	1.6	1.9	fmol
				18 - 99	YEARS - YEARS	33.0	36.0	fmol
				18 - 99	YEARS - YEARS	1.7	2.0	fmol
				6 - 12	YEARS - YEARS	1.5	1.9	fmol
				18 - 99	YEARS - YEARS	1.7	2.1	fmol
				0 - 99	YEARS - YEARS	1.6	2.1	fmol
				0 - 99	YEARS - YEARS	1.6	2.0	fmol
				0 - 99	YEARS - YEARS	1.6	2.0	fmol
				0 - 99	YEARS - YEARS	1.7	2.1	fmol
				0 - 99	YEARS - YEARS	1.8	2.3	fmol
				0 - 99	YEARS - YEARS	27.0	31.0	fmol
				0 - 99	YEARS - YEARS	28.0	33.0	fmol
				18 - 99	YEARS - YEARS	1.6	1.9	fmol
				6 - 7	YEARS - YEARS	1.5	1.8	fmol
				18 - 99	YEARS - YEARS	1.6	2.1	fmol

Listing of laboratory reference ranges

Continued...

Category	Parameter	Substance	LabID	Age range	Age range unit	Reference range lower limit (char)	Reference range upper limit (char)	Analysis unit
Haematology	MCH		[redacted]	18 - 99	YEARS - YEARS	1.7	1.9	fmol
	Platelets			0 - 120	YEARS - YEARS	130	360	10^9/L
				0 - 99	YEARS - YEARS	150	400	10^9/L
				18 - 99	YEARS - YEARS	140	360	10^9/L
				6 - 18	YEARS - YEARS	200	400	10^9/L
				0 - 99	YEARS - YEARS	150	400	10^9/L
				0 - 12	YEARS - YEARS	180	415	10^9/L
				0 - 99	YEARS - YEARS	140	440	10^9/L
				0 - 99	YEARS - YEARS	150	450	10^9/L
				0 - 99	YEARS - YEARS	150	400	10^9/L
				0 - 99	YEARS - YEARS	150	450	10^9/L
					YEARS - YEARS	150	450	
				6 - 99	YEARS - YEARS	150	400	10^9/L
				0 - 99	YEARS - YEARS	150	400	10^9/L
				18 - 99	YEARS - YEARS	151	304	10^9/L
				6 - 7	YEARS - YEARS	206	369	10^9/L
				6 - 99	YEARS - YEARS	150	410	10^9/L
				18 - 99	YEARS - YEARS	143	400	10^9/L
				18 - 99	YEARS - YEARS	140	440	10^9/L
	Packed Cell volume			16 - 120	YEARS - YEARS	40.0	53.0	%
				0 - 99	YEARS - YEARS	38.0	50.0	%
				0 - 99	YEARS - YEARS	40.0	54.0	%
				10 - 15	YEARS - YEARS	36.0	44.0	%
				13 - 16	YEARS - YEARS	34.7	46.2	%
				18 - 99	YEARS - YEARS	40.0	53.0	%
				18 - 99	YEARS - YEARS	40.0	52.0	%
				6 - 12	YEARS - YEARS	37.0	43.0	%
				18 - 99	YEARS - YEARS	0.4	0.5	%
				0 - 99	YEARS - YEARS	38.0	52.0	%
				0 - 15	YEARS - YEARS	36.5	47.5	%
				0 - 99	YEARS - YEARS	42.0	52.0	%
				0 - 99	YEARS - YEARS	37.0	52.0	%
				0 - 99	YEARS - YEARS	36.0	51.0	%
				0 - 99	YEARS - YEARS	0.4	0.5	%
					YEARS - YEARS	0.4	0.5	

Listing of laboratory reference ranges

Continued...

Category	Parameter	Substance	LabID	Age range	Age range unit	Reference range lower limit (char)	Reference range upper limit (char)	Analysis unit
Haematology	Packed Cell volume		[redacted]	18 - 99	YEARS - YEARS	0.4	0.5	%
				0 - 99	YEARS - YEARS	40.0	52.0	%
				18 - 99	YEARS - YEARS	0.4	0.5	%
				18 - 99	YEARS - YEARS	40.0	54.0	%
	Absolute cd4+			18 - 99	YEARS - YEARS	542.0	1570	1/uL
				0 - 99	YEARS - YEARS	600.0	1400	1/uL
Haematology	Neutrophils			6 - 120	YEARS - YEARS	40	75	%
				18 - 99	YEARS - YEARS	40	75	%
				12 - 99	YEARS - YEARS	40	75	%
				0 - 99	YEARS - YEARS	40	74	%
				12 - 99	YEARS - YEARS	43	76	%
				0 - 99	YEARS - YEARS	50	75	%
				18 - 99	YEARS - YEARS	40	74	%
	Lymphocytes			6 - 120	YEARS - YEARS	15	50	%
				18 - 99	YEARS - YEARS	18	48	%
				18 - 99	YEARS - YEARS	13	45	%
				0 - 99	YEARS - YEARS	25	45	%
				0 - 99	YEARS - YEARS	19	48	%
				12 - 99	YEARS - YEARS	17	41	%
				0 - 99	YEARS - YEARS	25	45	%
				18 - 99	YEARS - YEARS	19	48	%
	Monocytes			2 - 120	YEARS - YEARS	4	10	%
				18 - 99	YEARS - YEARS	4	11	%
				18 - 99	YEARS - YEARS	4	8	%
				0 - 99	YEARS - YEARS	2	8	%
				0 - 99	YEARS - YEARS	3	9	%
				2 - 99	YEARS - YEARS	3	9	%
				0 - 99	YEARS - YEARS	2	11	%
				18 - 99	YEARS - YEARS	3	9	%
	Eosinophils			0 - 120	YEARS - YEARS	0.0	5.0	%
				18 - 99	YEARS - YEARS	0.9	8.4	%
				12 - 99	YEARS - YEARS	0.0	5.0	%

Listing of laboratory reference ranges

Continued...

Category	Parameter	Substance	LabID	Age range	Age range unit	Reference range lower limit (char)	Reference range upper limit (char)	Analysis unit
Haematology	Eosinophils		[redacted]	0 - 99	YEARS - YEARS	1.0	4.0	%
				0 - 99	YEARS - YEARS	0.5	7.0	%
				0 - 99	YEARS - YEARS	0.0	5.0	%
				0 - 99	YEARS - YEARS	2.0	4.0	%
				18 - 99	YEARS - YEARS	0.2	5.0	%
	Basophils			0 - 120	YEARS - YEARS	0.0	1.0	%
				18 - 99	YEARS - YEARS	0.0	1.5	%
				6 - 99	YEARS - YEARS	0.0	1.0	%
				0 - 99	YEARS - YEARS	0.0	1.0	%
				0 - 99	YEARS - YEARS	0.0	1.5	%
				0 - 99	YEARS - YEARS	0.0	1.5	%
				0 - 99	YEARS - YEARS	0.0	1.0	%
				18 - 99	YEARS - YEARS	0.2	1.0	%
Antibodies	FVIII Neutralizing Ab			0 - 99	YEARS - YEARS	0.0	0.5	BU/mL
				18 - 99	YEARS - YEARS	0.0	0.6	BU/mL
				0 - 99	YEARS - YEARS	-99.0	0.3	BU/mL
				0 - 99	YEARS - YEARS	0	<0.6	BU/mL
					YEARS - YEARS	0	<0.6	
				0 - 99	YEARS - YEARS	0.1	0.6	BU/mL
				0 - 99	YEARS - YEARS	-99.0	0.4	BU/mL
				0 - 99	YEARS - YEARS	0.0	0.3	BU/mL
					YEARS - YEARS	0.0	0.3	
				18 - 99	YEARS - YEARS		<0.6	BU/mL
				6 - 7	YEARS - YEARS		<0.6	BU/mL
				18 - 99	YEARS - YEARS		0.5	BU/mL
				18 - 99	YEARS - YEARS		<0.6	BU/mL
				0 - 99	YEARS - YEARS	-99.0	0.5	BU/mL
				18 - 99	YEARS - YEARS		0.4	BU/mL
				0 - 99	YEARS - YEARS	-99.0	0.3	BU/mL
Coagulation	N8			0 - 199	YEARS - YEARS	70.0	150.0	IU/mL
				18 - 99	YEARS - YEARS	0.0	100.0	IU/mL
				0 - 99	YEARS - YEARS	60.0	150.0	IU/mL
				0 - 99	YEARS - YEARS	60.0	150.0	IU/mL
					YEARS - YEARS	60.0	150.0	

Listing of laboratory reference ranges

Continued...

Category	Parameter	Substance	LabID	Age range	Age range unit	Reference range lower limit (char)	Reference range upper limit (char)	Analysis unit
Haematology	FVIII		[redacted]	0 - 199	YEARS - YEARS	70.0	150.0	%
				0 - 99	YEARS - YEARS	50.0	150.0	%
				0 - 99	YEARS - YEARS	60.0	150.0	%
				0 - 99	YEARS - YEARS	50.0	200.0	%
				0 - 99	YEARS - YEARS	70.0	100.0	%
				18 - 99	YEARS - YEARS	64.00	104.0	IU/mL
				0 - 99	YEARS - YEARS	70.0	150.0	%
				0 - 99	YEARS - YEARS	80.0	120.0	%
				0 - 99	YEARS - YEARS	60.0	150.0	%
				0 - 99	YEARS - YEARS	50.0	150.0	%
				0 - 99	YEARS - YEARS	60.0	160.0	%
				0 - 99	YEARS - YEARS	60.0	150.0	%
					YEARS - YEARS	60.0	150.0	
				18 - 99	YEARS - YEARS	3.0	5.0	%
				18 - 99	YEARS - YEARS	50.0	150.0	%
				6 - 7	YEARS - YEARS	50.0	150.0	%
				18 - 99	YEARS - YEARS	50.0	200.0	%
				18 - 99	YEARS - YEARS	70.0	150.0	%
				6 - 99	YEARS - YEARS	50.0	150.0	%

14.3.4.2 Listing of limits of quantification

Laboratory parameter	LabID	LLOQ Threshold		LLOQ Unit		LLOQ Truncation Value	ULOQ Threshold	ULOQ Unit	ULOQ Truncation Value
		Original	Converted	Original	Converted				
ALAT	[redacted]	<50.00	<50.00	IU/mL	IU/L	25	-	-	-
Aspartate aminotransferase		<50.00	<50.00	IU/mL	IU/L	25	-	-	-
FVIII		<1.00	<1.00	%	%	0.5	-	-	-
		<0.70	<0.70	%	%	0.35	-	-	-
		<1.00	<1.00	%	%	0.5	-	-	-
		<0.1	<0.1	BU		0.05	-	-	-
		<1.00	<1.00	%	%	0.5	-	-	-
		<1.00	<1.00	%	%	0.5	-	-	-
		<1.00	<1.00	%	%	0.5	-	-	-
FVIII Neutralizing Ab		<0.6	<0.6	BU	BU/mL	0.3	-	-	-
		<1.0	<1.0	BU	BU/mL	0.5	-	-	-
		<0.6	<0.6	BU	BU/mL	0.3	-	-	-
		<0.40	<0.40	BU	BU/mL	0.2	-	-	-
		<0.40	<0.40	BU/mL	BU/mL	0.2	-	-	-
		<0.4	<0.4	BU	BU/mL	0.2	-	-	-
		<0.40	<0.40	BU	BU/mL	0.2	-	-	-
		<0.40	<0.40	BU/mL	BU/mL	0.2	-	-	-
		<00.40	<00.40	BU/mL	BU/mL	0.2	-	-	-
		<1.0	<1.0	BU	BU/mL	0.5	-	-	-
		<1.0	<1.0	BU	BU/mL	0.5	-	-	-
		<0.5	<0.5	BU/mL	BU/mL	0.25	-	-	-
		<0.6	<0.6	BU/mL	BU/mL	0.3	-	-	-
		<0.40	<0.40	BU	BU/mL	0.2	-	-	-
		<0.6	<0.6	BU	BU/mL	0.3	-	-	-
		<0.6	<0.6	BU	BU/mL	0.3	-	-	-
		<0.4	<0.4	BU/mL	BU/mL	0.2	-	-	-
		<0.40	<0.40	BU/mL	BU/mL	0.2	-	-	-
		<0.6	<0.6	BU	BU/mL	0.3	-	-	-
N8		<0.013	<0.013	IU/mL	IU/mL	0.0065	-	-	-
Serum GGT		<005.00	<005.00	U/L	IU/L	3	-	-	-
		<60.00	<60.00	IU/mL	IU/L	30	-	-	-
Total proteins		<5.00	<5.00	g/L	g/L	3	-	-	-

Listing of limits of quantification

Laboratory parameter	LabID	LLOQ Threshold		LLOQ Unit		LLOQ Truncation Value	ULOQ Threshold	ULOQ Unit	ULOQ Truncation Value
		Original	Converted	Original	Converted				

LLOQ: lower limit of quantification, ULOQ: upper limit of quantification.

14.3.4.3 Listing of haematology results outside reference range - safety analysis set

Patient ID/ Age group/ Severity	Laboratory parameter	Analysis date and time	Visit	Original result and unit	Converted result and unit	Converted reference ranges	Flag*	AF
[redacted]								

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

nn7008-3553/ctr_20201215_er - 15DEC2020 - l_1434_lab.sas/14340030_haemout.txt

Listing of haematology results outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Analysis date and time	Visit	Original result and unit	Converted result and unit	Converted reference ranges	Flag*	AF
[redacted]								

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

Listing of haematology results outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Analysis date and time	Visit	Original result and unit	Converted result and unit	Converted reference ranges	Flag*	AF
[redacted]								

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

Listing of haematology results outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Analysis date and time	Visit	Original result and unit	Converted result and unit	Converted reference ranges	Flag*	AF
[redacted]								

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

Listing of haematology results outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Analysis date and time	Visit	Original result and unit	Converted result and unit	Converted reference ranges	Flag*	AF
[redacted]								

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

Listing of haematology results outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Analysis date and time	Visit	Original result and unit	Converted result and unit	Converted reference ranges	Flag*	AF
[redacted]								

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

Listing of haematology results outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Analysis date and time	Visit	Original result and unit	Converted result and unit	Converted reference ranges	Flag*	AF
[redacted]								

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

Listing of haematology results outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Analysis date and time	Visit	Original result and unit	Converted result and unit	Converted reference ranges	Flag*	AF
[redacted]								

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

Listing of haematology results outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Analysis date and time	Visit	Original result and unit	Converted result and unit	Converted reference ranges	Flag*	AF
[redacted]								

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

Listing of haematology results outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Analysis date and time	Visit	Original result and unit	Converted result and unit	Converted reference ranges	Flag*	AF
[redacted]								

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

Listing of haematology results outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Analysis date and time	Visit	Original result and unit	Converted result and unit	Converted reference ranges	Flag*	AF
[redacted]								

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

Listing of haematology results outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Analysis date and time	Visit	Original result and unit	Converted result and unit	Converted reference ranges	Flag*	AF
[redacted]								

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

Listing of haematology results outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Analysis date and time	Visit	Original result and unit	Converted result and unit	Converted reference ranges	Flag*	AF
[redacted]								

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

Listing of haematology results outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Analysis date and time	Visit	Original result and unit	Converted result and unit	Converted reference ranges	Flag*	AF
[redacted]								

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

14.3.4.4 Listing of biochemistry results outside reference range - safety analysis set

Patient ID/ Age group/ Severity	Laboratory parameter	Analysis date and time	Visit	Original result and unit	Converted result and unit	Converted reference ranges	Flag*	AF
[redacted]								

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

nn7008-3553/ctr_20201215_er - 15DEC2020 - l_1434_lab.sas/14340040_bioout.txt

Listing of biochemistry results outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Analysis date and time	Visit	Original result and unit	Converted result and unit	Converted reference ranges	Flag*	AF
[redacted]								

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

Listing of biochemistry results outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Analysis date and time	Visit	Original result and unit	Converted result and unit	Converted reference ranges	Flag*	AF
[redacted]								

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

Listing of biochemistry results outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Analysis date and time	Visit	Original result and unit	Converted result and unit	Converted reference ranges	Flag*	AF
[redacted]								

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

Listing of biochemistry results outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Analysis date and time	Visit	Original result and unit	Converted result and unit	Converted reference ranges	Flag*	AF
[redacted]								

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

14.3.4.5 Vital signs outside reference range - safety analysis set

Patient ID/ Age group/ Severity	Parameter	Visit	Collection date	Result	Unit	Flag*
[redacted]						

*Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
nn7008-3553/ctr_20201215_er - 15DEC2020 - l_1434_vsout.sas/14340050_vsout.txt

Vital signs outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Parameter	Visit	Collection date	Result	Unit	Flag*
[redacted]						

*Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.

14.3.4.6 Factor VIII activity outside reference range - safety analysis set

Patient ID/ Age group/ Severity	Laboratory parameter	Visit	Collection date	Original		Converted				
				Result	Unit	Result	Unit	Reference range	Flag*	AF
[redacted]										

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

nn7008-3553/ctr_20201215_er - 15DEC2020 - l_1434_fviii.sas/14340060_fviiiout.txt

Factor VIII activity outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Visit	Collection date	Original		Converted				
				Result	Unit	Result	Unit	Reference range	Flag*	AF
[redacted]										

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

Factor VIII activity outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Visit	Collection date	Original		Converted				
				Result	Unit	Result	Unit	Reference range	Flag*	AF
[redacted]										

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

Factor VIII activity outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Visit	Collection date	Original		Converted				
				Result	Unit	Result	Unit	Reference range	Flag*	AF
[redacted]										

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

Factor VIII activity outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Visit	Collection date	Original		Converted				
				Result	Unit	Result	Unit	Reference range	Flag*	AF
[redacted]										

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

Factor VIII activity outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Visit	Collection date	Original		Converted				
				Result	Unit	Result	Unit	Reference range	Flag*	AF
[redacted]										

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

Factor VIII activity outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Visit	Collection date	Original		Converted				
				Result	Unit	Result	Unit	Reference range	Flag*	AF
[redacted]										

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

Factor VIII activity outside reference range - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Laboratory parameter	Visit	Collection date	Original		Converted				
				Result	Unit	Result	Unit	Reference range	Flag*	AF
[redacted]										

* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
AF: analysis flag, ND: not done, NA: not applicable.

14.3.5 Laboratory value displays

14.3.5.1 Factor VIII trough levels (%) for Baseline and last visit by age at inclusion - safety analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Visit 1 baseline			
N	4	30	34
Mean (SD)	1.4 (1.6)	6.9 (10.3)	6.2 (9.9)
Median	0.8	1.2	1.0
Min ; Max	0.4 ; 3.8	0.0 ; 38.0	0.0 ; 38.0
Last visit			
N	5	38	43
Mean (SD)	2.8 (4.1)	6.3 (9.1)	5.9 (8.7)
Median	1.0	1.8	1.6
Min ; Max	0.5 ; 10.0	0.0 ; 33.2	0.0 ; 33.2
Change (SD)	3.1 (4.4)	-0.5 (12.2)	-0.2 (11.8)

Last visit is defined as the last available visit after the baseline visit with a valid observation.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1435_lab.sas/14350010_fviiitage.txt

14.3.5.2 Factor VIII trough levels (%) for Baseline and last visit by haemophilia severity at inclusion - safety analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Visit 1 baseline			
N	29	4	34
Mean (SD)	6.3 (9.8)	7.2 (12.4)	6.2 (9.9)
Median	1.0	1.3	1.0
Min ; Max	0.0 ; 38.0	0.4 ; 25.7	0.0 ; 38.0
Last visit			
N	38	4	43
Mean (SD)	5.1 (7.5)	14.8 (15.8)	5.9 (8.7)
Median	1.4	12.8	1.6
Min ; Max	0.0 ; 26.7	0.4 ; 33.2	0.0 ; 33.2
Change (SD)	-1.5 (10.8)	9.3 (19.3)	-0.2 (11.8)

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
Last visit is defined as the last available visit after the baseline visit with a valid observation.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1435_lab.sas/14350020_fviiitfviii.txt

14.3.5.3 Factor VIII recovery levels (%) for Baseline and last visit by age at inclusion - safety analysis

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Visit 1 baseline			
N		9	9
Mean (SD)		80.4 (22.7)	80.4 (22.7)
Median		85.0	85.0
Min ; Max		38.0 ; 119.0	38.0 ; 119.0
Last visit			
N	2	9	11
Mean (SD)	92.8 (23.9)	58.8 (45.2)	65.0 (43.4)
Median	92.8	80.0	80.0
Min ; Max	75.9 ; 109.7	1.0 ; 123.0	1.0 ; 123.0
Change (SD)	0.0 (0.0)	6.0 (19.0)	4.9 (17.2)

Last visit is defined as the last available visit after the baseline visit with a valid observation.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1435_lab.sas/14350030_fviiirage.txt

14.3.5.4 Factor VIII recovery levels (%) for Baseline and last visit by haemophilia severity at inclusion -

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Visit 1 baseline			
N	7	2	9
Mean (SD)	77.0 (24.8)	92.2 (7.4)	80.4 (22.7)
Median	81.0	92.2	85.0
Min ; Max	38.0 ; 119.0	87.0 ; 97.4	38.0 ; 119.0
Last visit			
N	10	1	11
Mean (SD)	62.6 (44.9)	89.6 (-)	65.0 (43.4)
Median	78.0	89.6	80.0
Min ; Max	1.0 ; 123.0	89.6 ; 89.6	1.0 ; 123.0
Change (SD)	6.2 (17.6)	-7.8 (-)	4.9 (17.2)

Last visit is defined as the last available visit after the baseline visit with a valid observation.
Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1435_lab.sas/14350040_fviiirfviii.txt

14.3.5.5 FVIII inhibitors (BU) for Baseline and last visit by age at inclusion - safety analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Visit 1 baseline, N (%)			
Negative	12 (85.7)	45 (83.3)	57 (83.8)
Last visit, N (%)			
Negative	11 (78.6)	43 (79.6)	54 (79.4)

Last visit is defined as the last available visit after the baseline visit with a valid observation.
BU/mL: Bethesda units/mL.
FVIII inhibitors were measured using the Nijmegen modification of the Bethesda assay.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1435_lab_inhib.sas/14350050_inhage.txt

14.3.5.6 FVIII inhibitors (BU) for Baseline and last visit by haemophilia severity at inclusion - safety analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Visit 1 baseline, N (%)			
Negative	52 (89.7)	4 (44.4)	57 (83.8)
Last visit, N (%)			
Negative	48 (82.8)	5 (55.6)	54 (79.4)

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
Last visit is defined as the last available visit after the baseline visit with a valid observation.
BU/mL: Bethesda units/mL.
FVIII inhibitors were measured using the Nijmegen modification of the Bethesda assay.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1435_lab_inhib.sas/14350060_inhfviii.txt

14.3.6 Other safety observations displays

14.3.6.1 Pulse (Beats/Min) for Baseline and last visit by age at inclusion - safety analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Visit 1 baseline			
N	12	31	43
Mean (SD)	81.8 (12.2)	72.0 (9.7)	74.8 (11.2)
Median	83.5	72.0	74.0
Min ; Max	60.0 ; 96.0	48.0 ; 90.0	48.0 ; 96.0
Last visit			
N	10	31	41
Mean (SD)	80.8 (4.1)	75.7 (9.6)	77.0 (8.8)
Median	81.0	76.0	78.0
Min ; Max	76.0 ; 86.0	60.0 ; 96.0	60.0 ; 96.0
Change (SD)	-1.8 (9.8)	4.5 (12.1)	2.6 (11.7)

Last visit is defined as the last available visit after the baseline visit with a non-missing value.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1436_vs.sas/14360010_pulseage.txt

14.3.6.2 Pulse (Beats/Min) for Baseline and last visit by haemophilia severity at inclusion - safety analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Visit 1 baseline			
N	37	6	43
Mean (SD)	75.0 (10.7)	73.2 (15.1)	74.8 (11.2)
Median	74.0	74.5	74.0
Min ; Max	48.0 ; 96.0	52.0 ; 90.0	48.0 ; 96.0
Last visit			
N	36	5	41
Mean (SD)	76.1 (8.2)	83.2 (11.6)	77.0 (8.8)
Median	76.5	86.0	78.0
Min ; Max	60.0 ; 90.0	66.0 ; 96.0	60.0 ; 96.0
Change (SD)	1.3 (10.3)	16.0 (19.1)	2.6 (11.7)

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
Last visit is defined as the last available visit after the baseline visit with a non-missing value.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1436_vs.sas/14360020_pulsefviii.txt

14.3.6.3 Systolic blood pressure (mmHg) for Baseline and last visit by age at inclusion - safety analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Visit 1 baseline			
N	12	34	46
Mean (SD)	99.4 (12.0)	131.4 (11.7)	123.0 (18.4)
Median	96.5	130.0	126.5
Min ; Max	85.0 ; 125.0	110.0 ; 170.0	85.0 ; 170.0
Last visit			
N	10	35	45
Mean (SD)	97.1 (5.1)	128.0 (13.5)	121.2 (17.7)
Median	95.5	125.0	122.0
Min ; Max	90.0 ; 109.0	105.0 ; 180.0	90.0 ; 180.0
Change (SD)	1.8 (5.4)	-3.3 (12.1)	-1.9 (10.9)

Last visit is defined as the last available visit after the baseline visit with a non-missing value.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1436_vs.sas/14360030_sysage.txt

14.3.6.4 Systolic blood pressure (mmHg) for Baseline and last visit by haemophilia severity at inclusion - safety analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Visit 1 baseline			
N	39	7	46
Mean (SD)	122.0 (18.4)	128.7 (18.4)	123.0 (18.4)
Median	125.0	133.0	126.5
Min ; Max	85.0 ; 170.0	96.0 ; 150.0	85.0 ; 170.0
Last visit			
N	38	7	45
Mean (SD)	120.9 (17.5)	122.3 (20.7)	121.2 (17.7)
Median	122.5	119.0	122.0
Min ; Max	90.0 ; 180.0	95.0 ; 150.0	90.0 ; 180.0
Change (SD)	-2.0 (11.6)	-1.4 (4.4)	-1.9 (10.9)

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
Last visit is defined as the last available visit after the baseline visit with a non-missing value.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1436_vs.sas/14360040_sysfviii.txt

14.3.6.5 Diastolic blood pressure (mmHg) for Baseline and last visit by age at inclusion - safety analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Visit 1 baseline			
N	12	34	46
Mean (SD)	66.4 (6.0)	77.9 (12.4)	74.9 (12.1)
Median	65.0	79.5	75.0
Min ; Max	55.0 ; 75.0	43.0 ; 120.0	43.0 ; 120.0
Last visit			
N	10	35	45
Mean (SD)	66.7 (7.7)	78.3 (12.0)	75.8 (12.1)
Median	67.5	80.0	78.0
Min ; Max	56.0 ; 80.0	39.0 ; 110.0	39.0 ; 110.0
Change (SD)	0.5 (7.3)	-0.2 (10.4)	-0.0 (9.6)

Last visit is defined as the last available visit after the baseline visit with a non-missing value.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1436_vs.sas/14360050_diaage.txt

14.3.6.6 Diastolic blood pressure (mmHg) for Baseline and last visit by haemophilia severity at inclusion - safety analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Visit 1 baseline			
N	39	7	46
Mean (SD)	74.4 (11.2)	77.6 (17.3)	74.9 (12.1)
Median	74.0	80.0	75.0
Min ; Max	55.0 ; 120.0	43.0 ; 100.0	43.0 ; 120.0
Last visit			
N	38	7	45
Mean (SD)	76.4 (10.8)	72.0 (18.6)	75.8 (12.1)
Median	78.0	70.0	78.0
Min ; Max	56.0 ; 110.0	39.0 ; 95.0	39.0 ; 110.0
Change (SD)	0.3 (10.2)	-2.2 (3.6)	-0.0 (9.6)

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
Last visit is defined as the last available visit after the baseline visit with a non-missing value.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1436_vs.sas/14360060_diafviii.txt

14.3.6.7 Body measurements - weight (kg) for Baseline and last visit by age at inclusion - safety analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Visit 1 baseline			
N	14	51	65
Mean (SD)	31.9 (13.1)	78.0 (15.7)	68.1 (24.4)
Median	28.6	80.0	72.0
Min ; Max	20.0 ; 63.0	37.6 ; 116.0	20.0 ; 116.0
Last visit			
N	13	50	63
Mean (SD)	32.6 (11.2)	80.2 (16.8)	70.4 (25.0)
Median	27.5	80.0	75.0
Min ; Max	22.0 ; 57.3	37.0 ; 127.0	22.0 ; 127.0
Change (SD)	2.4 (4.7)	2.1 (5.5)	2.2 (5.3)

Last visit is defined as the last available visit after the baseline visit with a non-missing value.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1436_vs.sas/14360070_weightage.txt

14.3.6.8 Body measurements - weight (kg) for Baseline and last visit by haemophilia severity at inclusion - safety analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Visit 1 baseline			
N	56	8	65
Mean (SD)	66.8 (24.3)	74.2 (25.3)	68.1 (24.4)
Median	72.0	71.0	72.0
Min ; Max	20.0 ; 116.0	43.3 ; 115.0	20.0 ; 116.0
Last visit			
N	53	9	63
Mean (SD)	68.9 (25.4)	76.6 (22.6)	70.4 (25.0)
Median	75.0	73.4	75.0
Min ; Max	22.0 ; 127.0	45.1 ; 120.0	22.0 ; 127.0
Change (SD)	2.2 (5.3)	2.0 (6.1)	2.2 (5.3)

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
Last visit is defined as the last available visit after the baseline visit with a non-missing value.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1436_vs.sas/14360080_weightfviii.txt

14.3.6.9 Body measurements - BMI (kg/m^2) for Baseline and last visit by age at inclusion - safety analysis set

	Baseline age < 12 years	Baseline age >= 12 years	Total
Number of patients	14	54	68
Visit 1 baseline			
N	14	50	64
Mean (SD)	17.4 (3.5)	25.4 (4.7)	23.6 (5.6)
Median	16.2	24.9	23.8
Min ; Max	13.4 ; 27.3	16.8 ; 38.9	13.4 ; 38.9
Last visit			
N	13	48	61
Mean (SD)	17.1 (2.5)	25.9 (5.4)	24.0 (6.1)
Median	16.9	25.1	23.8
Min ; Max	14.5 ; 22.7	18.1 ; 42.4	14.5 ; 42.4
Change (SD)	-0.0 (1.8)	0.5 (1.7)	0.4 (1.7)

Last visit is defined as the last available visit after the baseline visit with a non-missing value.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1436_vs.sas/14360090_bmiage.txt

14.3.6.10 Body measurements - BMI (kg/m^2) for Baseline and last visit by haemophilia severity at inclusion - safety analysis set

	Severe	Moderately Severe	Total
Number of patients	58	9	68
Visit 1 baseline			
N	56	7	64
Mean (SD)	23.2 (5.3)	25.9 (7.5)	23.6 (5.6)
Median	23.2	26.3	23.8
Min ; Max	13.4 ; 38.8	16.8 ; 38.9	13.4 ; 38.9
Last visit			
N	53	7	61
Mean (SD)	23.6 (5.8)	26.3 (7.6)	24.0 (6.1)
Median	23.4	25.1	23.8
Min ; Max	14.5 ; 42.4	18.5 ; 41.0	14.5 ; 42.4
Change (SD)	0.4 (1.8)	0.4 (1.3)	0.4 (1.7)

Severe: FVIII level <1%, Moderately Severe: FVIII level 1-2%.
1 patient with FVIII activity >2% at inclusion is included in the 'Total' column to represent the full analysis set.
Last visit is defined as the last available visit after the baseline visit with a non-missing value.
nn7008-3553/ctr_20201215_er - 15DEC2020 - t_1436_vs.sas/14360100_bmifviii.txt

14.3.7 Other safety observations listings

14.3.7.1 Vital signs - safety analysis set

Patient ID/ Age group/ Severity	Visit	Collection date	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Pulse (beats/min)
[redacted]					

ND: not done, NA: not applicable, NK: not known.

Vital signs - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Pulse (beats/min)
[redacted]					

ND: not done, NA: not applicable, NK: not known.

Vital signs - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Pulse (beats/min)
[redacted]					

ND: not done, NA: not applicable, NK: not known.

Vital signs - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Pulse (beats/min)
[redacted]					

ND: not done, NA: not applicable, NK: not known.

Vital signs - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Pulse (beats/min)
[redacted]					

ND: not done, NA: not applicable, NK: not known.

Vital signs - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Pulse (beats/min)
[redacted]					

ND: not done, NA: not applicable, NK: not known.

Vital signs - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Pulse (beats/min)
[redacted]					

ND: not done, NA: not applicable, NK: not known.

Vital signs - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Pulse (beats/min)
[redacted]					

ND: not done, NA: not applicable, NK: not known.

Vital signs - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Pulse (beats/min)
[redacted]					

ND: not done, NA: not applicable, NK: not known.

Vital signs - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Pulse (beats/min)
[redacted]					

ND: not done, NA: not applicable, NK: not known.

Vital signs - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Pulse (beats/min)
[redacted]					

ND: not done, NA: not applicable, NK: not known.

Vital signs - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Pulse (beats/min)
[redacted]					

ND: not done, NA: not applicable, NK: not known.

Vital signs - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Pulse (beats/min)
[redacted]					

ND: not done, NA: not applicable, NK: not known.

Vital signs - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Pulse (beats/min)
[redacted]					

ND: not done, NA: not applicable, NK: not known.

14.3.7.2 Body measurements - safety analysis set

Patient ID/ Age group/ Severity	Visit	Collection date	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]					

BMI: body mass index, ND: not done, NA: not applicable, NK: not known.

Body measurements - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]					

BMI: body mass index, ND: not done, NA: not applicable, NK: not known.

Body measurements - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]					

BMI: body mass index, ND: not done, NA: not applicable, NK: not known.

Body measurements - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]					

BMI: body mass index, ND: not done, NA: not applicable, NK: not known.

Body measurements - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]					

BMI: body mass index, ND: not done, NA: not applicable, NK: not known.

Body measurements - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]					

BMI: body mass index, ND: not done, NA: not applicable, NK: not known.

Body measurements - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]					

BMI: body mass index, ND: not done, NA: not applicable, NK: not known.

Body measurements - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]					

BMI: body mass index, ND: not done, NA: not applicable, NK: not known.

Body measurements - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]					

BMI: body mass index, ND: not done, NA: not applicable, NK: not known.

Body measurements - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]					

BMI: body mass index, ND: not done, NA: not applicable, NK: not known.

Body measurements - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]					

BMI: body mass index, ND: not done, NA: not applicable, NK: not known.

Body measurements - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]					

BMI: body mass index, ND: not done, NA: not applicable, NK: not known.

Body measurements - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]					

BMI: body mass index, ND: not done, NA: not applicable, NK: not known.

14.3.7.3 Physical examination by visit - safety analysis set

Patient ID/
Age group/
Severity Visit Collection date System Result Specify Abnormality CS

[redacted]

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

Physical examination by visit - safety analysis set

Continued...

Patient ID/ Age group/ Severity	Visit	Collection date	System	Result	Specify Abnormality	CS
[redacted]						

CS: Clinically significant, ND: not done, NA: not applicable.

15 References

1. World Medical Association. Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 59th WMA General Assembly, Seoul, Republic of Korea. October 2008.
2. ISPE (International Society for Pharmacoepidemiology). - Guidelines for Good Pharmacoepidemiology Practices (GPP). Revision 2, April, 2007.
3. White GC, 2nd, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J, et al. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. Thromb Haemost. 2001;85(3):560.
4. Vander AJ, Sherman JH, Luciano DS. Hemostasis:The Prevention of Blood Loss. In: Vander AJ, Sherman JH, Luciano DS, editors. Human Physiology. 6th ed: McGraw-Hill, Inc.; 1994. p. 741-50.
5. Manco-Johnson MJ, Abshire T, Brown D, buchanan GR, Cohen AR, DiMichele D, et al. Randomized, controlled, multi-year study to evaluate joint outcomes in young children using recombinant factor VIII (Kogenate FS). Haemophilia. 2006;12(suppl 2):12-22.
6. Thim L, Vandahl B, Karlsson J, Klausen NK, Pedersen J, Krogh TN, et al. Purification and characterization of a new recombinant factor VIII (N8). Haemophilia. 2010;16(2):349-59.
7. Christiansen ML, Balling KW, Persson E, Hilden I, Bagger-Sørensen A, Sørensen BB, et al. Functional characteristics of N8, a new recombinant FVIII. Haemophilia. 2010;16(6):878-87.
8. Iorio A, Halimeh S, Holzhauer S, Goldenberg N, Marchesini E, Marcucci M, et al. Rate of inhibitor development in previously untreated hemophilia A patients treated with plasma-derived or recombinant factor VIII concentrates: a systematic review. J Thromb Haemost. 2010;8(6):1256-65.
9. Boekhorst J, Lari GR, D'Oiron R, Costa JM, Novakova IR, Ala FA, et al. Factor VIII genotype and inhibitor development in patients with haemophilia A: highest risk in patients with splice site mutations. Haemophilia. 2008;14(4):729-35.
10. Oldenburg J, El-Maarri O, Schwaab R. Inhibitor development in correlation to factor VIII genotypes. Haemophilia. 2002;8 Suppl 2:23-9.
11. Lee C, Berntorp E, Hoots K. Textbook of Hemophilia. 2nd ed: Wiley-Blackwell. 2010.
12. Astermark J, Altisent C, Batorova A, Diniz MJ, Gringeri A, Holme PA, et al. Non-genetic risk factors and the development of inhibitors in haemophilia: a comprehensive review and consensus report. Haemophilia. 2010;16(5):747-66.
13. Gouw SC, van der Bom JG, Ljung R, Escuriola C, Cid AR, Claeyssens-Donadel S, et al. Factor VIII products and inhibitor development in severe hemophilia A. N Engl J Med. 2013;368(3):231-9.
14. Xi M, Makris M, Marcucci M, Santagostino E, Mannucci PM, Iorio A. Inhibitor development in previously treated hemophilia A patients: a systematic review, meta-analysis, and meta-regression. J Thromb Haemost. 2013;11(9):1655-62.
15. Hay CR, Palmer BP, Chalmers EA, Hart DP, Liesner R, Rangarajan S, et al. The incidence of factor VIII inhibitors in severe haemophilia A following a major switch from full-length to B-domain-deleted factor VIII: a prospective cohort comparison. Haemophilia. 2015;21(2):219-26.
16. Rubinger M, Lillicrap D, Rivard GE, Teitel J, Carcao M, Hensman C, et al. A prospective surveillance study of factor VIII inhibitor development in the Canadian haemophilia A population following the switch to a recombinant factor VIII product formulated with sucrose. Haemophilia. 2008;14(2):281-6.

17. Martinowitz U, Bjerre J, Brand B, Klamroth R, Misgav M, Morfini M, et al. Bioequivalence between two serum-free recombinant factor VIII preparations (N8 and ADVATE (R)) - an open-label, sequential dosing pharmacokinetic study in patients with severe haemophilia A. Haemophilia. 2011;17(6):854-9.
18. EMA. Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009 rev. 2). 1 February 2019.
19. EMA/CHMP/BPWP/144533/2009. Committee for Medicinal Products for Human Use (CHMP), Guideline on the Clinical Investigation of Recombinant and Human Plasma-derived Factor VIII Products. 2009 2009. p. 1-19.
20. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module VIII - Post-authorisation safety studies (EMA/813938/2011 Rev 3). 2017.
21. Oldenburg J, Goudemand J, Valentino L, Richards M, Luu H, Kriukov A, et al. Postauthorization safety surveillance of ADVATE [antihaemophilic factor (recombinant), plasma/albumin-free method] demonstrates efficacy, safety and low-risk for immunogenicity in routine clinical practice. Haemophilia. 2010;16(6):866-77.
22. Smith MP, Giangrande P, Pollman H, Littlewood R, Kollmer C, Feingold J, et al. A postmarketing surveillance study of the safety and efficacy of ReFacto (St Louis-derived active substance) in patients with haemophilia A. Haemophilia. 2005;11(5):444-51.
23. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, et al. Guidelines for the management of hemophilia. Haemophilia. 2013;19(1):e1-47.
24. Amby LK, Seremetis S, Obergfell A, Bjerre J. Challenges of defining reliable clinical surrogate end points in haemophilia trials: a critical review. Blood Coagul Fibrinolysis. 2009;20(7):488-93.

Appendices

Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	16.1.1	25 June 2020	Protocol and protocol amendments
2	16.1.2	25 June 2020	Sample case report form
3	16.1.3	25 June 2020	List of Independent Ethics Committees and/or Institutional Review Boards
4	16.1.4	25 June 2020	List and description of physicians in the study
5	16.1.5	08 January 2021	Signature of signatory physician
6	16.1.6	25 June 2020	Audit certificates
7	16.1.7	08 January 2021	Documentation of statistical methods
8	16.1.8	25 June 2020	Documentation of inter-laboratory standardisation methods and quality assurance
9	16.1.9	25 June 2020	Publications based on the study
10	16.1.10	25 June 2020	Important publications referenced in the report

Annex 2. Additional information

Number	Document reference number	Date	Title
1	16.2.1	08 January 2021	Discontinued patients
2	16.2.2	25 June 2020	Important protocol deviations
3	16.2.3	08 January 2021	Patients excluded from the efficacy analysis
4	16.2.4	08 January 2021	Demographic data
5	16.2.5	08 January 2021	Compliance and/or drug concentration data
6	16.2.6	08 January 2021	Individual efficacy response data
7	16.2.7	08 January 2021	Listings of adverse events (by patient) and/or technical complaints
8	16.2.8	08 January 2021	Listing of individual laboratory measurements by patient
9	16.3.1	25 June 2020	CRFs for deaths, other serious adverse events, and adverse event withdrawals
10	16.3.2	25 June 2020	Other CRFs submitted