Non-interventional study report

Study ID: NN1841-3868

Use of rFXIII in treatment of congenital FXIII deficiency, a prospective multi-centre observational study

mentor™6

PASS information

Title	Use of rFXIII in treatment of congenital FXIII deficiency, a prospective multi-centre observational study
Version identifier of the final study report	1.0
Date of last version of the final study report	05 December 2019
EU PAS register number	ENCEPP/SDPP/3687 EUPAS3687
EU PAS register link	http://www.encepp.eu/encepp/viewResource.htm?id=15534
Active substance	Catridecacog (recombinant coagulation factor XIII) [rFXIII] Antihaemorrhagics ATC code: B02BD11
Medicinal product	NovoThirteen® 2,500 IU Tretten® (Canada only) TRETTEN®
Product reference	EU/1/12/775/001 FDA BLA application number: 125398
Procedure number	EMEA/H/C/002284
Marketing authorisation holder	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark
Joint PASS	No
Research question and objectives	This study is designed to further explore the safety profile and the effectiveness of rFXIII in clinical practice. Primary objective: • The aim of this non-interventional study is to investigate the incidence of specific adverse drug reactions associated with the use of recombinant factor XIII (rFXIII) in patients with congenital FXIII A-subunit deficiency, comprising anti-FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of therapeutic effect. Secondary objectives: • To further explore the overall safety and effectiveness of rFXIII under conditions of routine clinical care in patients with congenital FXIII A-subunit deficiency, including special population (i.e., children, elderly,

	pregnant and lactating women, and patients with renal insufficiency). • To assess the use of rFXIII in patients with congenital FXIII A-subunit deficiency, also other than for prophylactic use. • To better understand the use of rFXIII and practice patterns in the usual care of patients.
Countries of study	Denmark, Canada, Spain, USA, United Kingdom, Hungary and Italy.
UTN	U1111-1131-1558
ClinicalTrials.gov identifier	NCT01862367
IND number	N/A
Generic name	Catridecacog (recombinant coagulation factor XIII)
Indication	Long term prophylactic treatment of bleeding in patients with congenital factor XIII A-subunit deficiency. NovoThirteen can be used for all age groups
Investigators	There were 17 principal investigators in the study, one at each study site. The signatory investigator for this report is: [redacted]
Study sites	The patients were enrolled at 17 sites in 7 countries: Denmark (4 patients), Canada (3 patients), Spain (3 patients), USA (13 patients), United Kingdom (1 patient), Hungary (1 patient) and Italy (5 patients).
Study initiated	17 May 2013 (First patient first visit [FPFV])
Study completed	26 June 2019 (Last patient last visit [LPLV])
Lead study manager	[redacted]
Medical specialist	
Epidemiologist/Biostatistician	
Report date	05 December 2019

Marketing authorisation holders

Marketing authorisation holder (MAH)	**Novo Nordisk A/S** **Novo Allé** **DK-2880 Bagsvaerd** **Denmark**
MAH contact person	[redacted] Novo Nordisk A/S, Denmark

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

Table of contents for the non-interventional study report

List of in-text tables

1 Abstract

This is available as a separate report.

2 List of abbreviations and definitions of terms

ADR	adverse drug reaction
ABR	annualised bleeding rate
CI	confidence interval
CRF	case report form
CT	computed tomography
EU	European Union
FPFV	first patient first visit
FXIII	Factor XIII
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LAR	legally acceptable representative
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
PASS	Post-authorisation Safety Study
PD	protocol deviation
PT	preferred term
PRO-RBDD	Prospective Rare Bleeding Disorder Database
rFXIII	recombinant factor XIII
SAE	serious adverse event
SOC	system organ class
W1	withdrawal criterion 1
W2	withdrawal criterion 2
W3	withdrawal criterion 3

3 Investigators

Please refer to Annex 16.1.4 for the list of investigators in this study.

4 Other responsible parties

This section is not applicable for the study.

5 Milestones

Table 5-1 Milestones

Milestone	Planned date	Actual date
Start of data collection	17 May 2013	17 May 2013
Registration in the EU PAS register	28 May 2013	28 May 2013
End of data collection for interim report 1	17 May 2015	17 May 2015
Interim report 1	30 October 2015	30 October 2015
End of data collection for interim report 2	17 May 2017	17 May 2017
Interim report 2	10 November 2017	10 November 2017
End of data collection for final report	29 June 2019	26 June 2019
Final report of study results	28 December 2019	05 December 2019

6 Rationale and background

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

The study was conducted in accordance with Good Pharmacovigilance Practice.

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). The IECs/IRBs were transparent in their functioning, independent of the researcher, the sponsor and any other undue influence, and duly qualified.

This study (referred to as mentor™6) was designed to observe the use of recombinant human coagulation factor XIII (rFXIII) in normal clinical practice and hereby further explore the safety profile and effectiveness of rFXIII. This study would expand the overall understanding of the safety profile of rFXIII. The emphasis was placed on adverse drug reactions (ADRs) of special interest comprising anti-FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of effect. The overall safety and effectiveness of rFXIII in patients with congenital FXIII A-subunit deficiency were explored under conditions of routine clinical care. The effectiveness of prophylactic treatment was assessed by the evaluation of the annualised rate of bleeding (ABR) (both non treatment-requiring bleeding episodes and treatment-requiring bleeding episodes).

In addition to results from the mentor™6 study, this report also includes results from the global Prospective Rare Bleeding Disorder Database (PRO-RBDD) registry. A contractual collaboration (02 February 2012 to 11 November 2018) with the registry had been established to collect data on patients with congenital FXIII A-subunit deficiency.

The PRO-RBDD is an international database collecting prospective clinical and laboratory data of patients with rare bleeding disorders in order to gather information on the incidence of bleeding episodes and consumption of treatment products.

Data was collected at:

- Baseline: clinical history reported at patient's enrolment.
- Follow-up: prospective data collection on any clinical event (bleeding, pregnancy, surgery), treatment, adverse events or complications, every 6 months for a duration of three years, later extended to five years.

7 Research question and objectives

This research study addressed the question, "What is the long-term safety and effectiveness of rFXIII in patients with congenital FXIII A-subunit deficiency and what are the current clinical treatment practices for rFXIII use".

As stated in the protocol and amendments, the objectives of the study were as follows:

Primary objective:

- The aim of this non-interventional study is to investigate the incidence of specific ADRs associated with the use of rFXIII in patients with congenital FXIII A-subunit deficiency, comprising anti-FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of therapeutic effect.

Secondary objectives*:*

- To further explore the overall safety and effectiveness of rFXIII under conditions of routine clinical care in patients with congenital FXIII A-subunit deficiency, including special population (i.e., children, elderly, pregnant and lactating women, and patients with renal insufficiency).
- To assess the use of rFXIII in patients with congenital FXIII A-subunit deficiency, also other than for prophylactic use.
- To better understand the use of rFXIII and practice patterns in the usual care of patients.

8 Amendments and updates

There were 4 amendments to the study protocol after the start of data collection in this study. Amendment no. 1 was done before FPFV.

Table 8-1 Amendments to the protocol

Date	Section of study protocol	Amendment or update	Reason
11 January 2013 (amendment no 1)[a]	Section 2	For analysis of human EDTA plasma requires approximately 2 mL whole blood (0.5-1 mL EDTA plasma).	Change of collected volume of blood (optional blood sample) taken at the Visit 1 for FXIII activity samples from 1 mL for the blood collection to 2 mL blood was needed to be collected for the FXIII activity analysis
22 January 2014 (amendment no.2)	Section 2.4 (section 8.1/visit procedures, 8.3/Assessments for safety and 15.2.3/Baseline characteristics) and accordingly in the flow chart section 2.2 (section 2)	To collect blood samples for testing of anti-factor XIII antibodies at visit 1 and at a visit to be conducted 1 year after entry of the patient into the study	FDA Post approval commitment to ensure data on FXIII antibody development from as many patients as possible
04 February 2014 (amendment no.3)	Throughout the whole protocol	Withdrawn internally by Novo Nordisk.	Main rationale for preparing this amendment was clarifications with regards to wording in the Updated Protocol, no. 2, dated 22 January 2014.
11 August 2014 (amendment no.4)	Throughout the whole protocol	The main rationale for amending the protocol is due to EMA has published new requirements for non-interventional PASS (EMA/623947/2012) studies regarding protocol format and content.	The update of the protocol to the EMA/PRAC (Pharmacovigilance Risk Assessment Committee) required protocol template is not a strict regulatory requirement but is encouraged for PASS protocols submitted before 10 January 2013 (the original mentor™6 protocol was submitted to EMA for assessment in June 2012).

Date	Section of study protocol	Amendment or update	Reason
02 February 2016 (amendment no.5)	Section 2 PASS information, Section 3 Responsible parties, Section 4.1 Title, Section 4.3 Primary endpoint, Secondary endpoints, Section 4.5 Population, Section 4.8 Study size, Section 4.10 Milestones, Section 6 Milestones, Section 8.2.1 Primary endpoint, Section 8.2.2 Secondary endpoints, Section 9.1.1 Type of study, Section 9.1.2 Rationale for study design, Section 9.1.3 Treatment of patients, Section 9.3.2.7 Concomitant illnesses, Section 9.5 Study size, Section 9.7.2.2 Secondary endpoints.	Recruitment period extended with 1 year to 17 May 2017. Definition of concomitant illness updated. Minor administrative changes implemented.	With the current recruitment rate, it will not be possible to reach the anticipated number of 30 patients within the current recruitment period. Definition of concomitant illness aligned with other trials/studies in the project.

Note: [a] amendment no. 1 is dated before first patient first visit (11 January 2013)

Abbreviations: EMA= European Medicine Agency; FDA= Food and Drug Administration; PASS= Post-authorisation Safety Study

9 Research methods

9.1 Study design

Rationale

This was a prospective, single-arm, multi-centre and multinational non-interventional post-authorisation safety study (PASS) related to treatment with rFXIII in patients with congenital FXIII A-subunit deficiency. No controls or blinding procedures were applied.

The rationale for choosing this study design was to assess safety related to treatment with rFXIII in a real-world setting in patients with congenital FXIII A-subunit deficiency. The multi-centre design chosen was to ensure sufficient screening pool of patients for the study. The multinational approach was selected to account for possible variations related to ethnic groups.

The total study duration was 6 years which was considered an appropriate and reasonable time allowing for further expansion of the known safety of rFXIII for the treatment of patients with congenital FXIII A-subunit deficiency. The end of study visit was performed 6 years after FPFV in the study. The patients' next visit to the clinic was defined as their end of study visit, provided they have either a minimum of 2 years participation or 24 exposure days (whichever came first, unless the patient had dropped out).

Due to the rarity of the disease and very limited available data with regards to rare adverse events, a systematic sample size calculation was not feasible. It was acknowledged that the small target population limited the potential for enrolment and not all of the diagnosed patients have a current need for treatment of their congenital FXIII A-subunit deficiency. The availability of patients for enrolment in the study would also be determined by market uptake of rFXIII for prophylactic treatment of patients with congenital FXIII A-subunit deficiency.

Description of study visits

The study consisted of the following visits:

- Visit 1: A blood sample for anti-rFXIII antibodies was taken for patients consenting to testing in countries where the collection of blood samples for anti-rFXIII antibody assessment was possible within the confines of a non-interventional study.
- Assessment visits (visit 2.1, 2.2 etc.)
- End of study visit (visit 3)

Please refer to Section 9.3.1 of the protocol for more details on the visits.

Endpoints

Primary endpoint

The incidence of specific ADRs in patients with congenital FXIII A-subunit deficiency treated with rFXIII, comprising anti-FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of effect, collected during a study period of up to 6 years.

Secondary endpoint

- All serious adverse events (SAE) collected during a study period of up to 6 years[a]
- All medical events of special interest collected during a study period of up to 6 years[a]
- All medication errors and near medication errors collected during a study period of up to 6 years.[a, b]
- Use of rFXIII in patients with congenital FXIII A-subunit deficiency, also for other uses than for prophylactic treatment collected during a study period of up to 6 years.
- ABR collected during a study period of up to 6 years.

[a] The first three secondary endpoints will be presented by all patients as well as by special populations comprising children, elderly, pregnant and lactating women, and patients with renal insufficiency.

[b] Medication errors and near medication errors are a subset of the medical events of special interest

9.2 Setting

This study was conducted in a real-world setting in patients with congenital FXIII A-subunit deficiency. The multi-centre, multinational design was chosen to ensure sufficient heterogeneous population of patients for the study. The study was conducted in 7 countries with 17 active sites. The study was initiated with first patient first visit (FPFV) on 17 May 2013 and last patient last visit (LPLV) was 26 June 2019.

9.3 Patients and study size

This study included patients with congenital FXIII A-subunit deficiency for whom the decision to treat with rFXIII had been made prior to including patients in the study.

The study aimed at observing all patients exposed to rFXIII in the EU, and additional patients from selected non-EU countries including Canada and the USA. Hence, in combination with the patients recruited outside Europe, a minimum of 30 patients were anticipated to be enrolled in the study. Such an anticipated minimum number of patients were judged to facilitate a sufficient expansion to the safety experience of prophylactic treatment with rFXIII, taking into consideration the rarity of the disease.

No formal analysis of sample size was conducted, but the adequacy of an expected number of patients had been considered.

The patients were enrolled at 17 sites in 7 countries: Denmark (4 patients), Canada (3 patients), Spain (3 patients), USA (13 patients), United Kingdom (1 patient), Hungary (1 patient) and Italy (5 patients).

Challenges in recruiting patients

It was acknowledged that the small target population limits the potential for enrolment and not all of the diagnosed patients have a current need for treatment of their congenital FXIII A-subunit deficiency. The availability of patients for enrolment in the study was also determined by the market uptake of rFXIII for prophylactic treatment of patients with congenital FXIII A-subunit deficiency.

The market penetration of rFXIII for the treatment of congenital FXIII A subunit deficiency also determined the number of patients eligible for inclusion in this study.

9.3.1 Diagnosis and main criteria for inclusion

- Informed consent obtained before any study-related activities (study-related activities are any procedure related to recording of data according to the protocol).
- Able and willing to provide signed informed consent (or patient's legally acceptable representative [LAR] consent, if applicable), as required by local ethics committee, governmental or regulatory authorities.
- Congenital FXIII A-subunit deficiency.
- Actual or planned exposure to the rFXIII.

Diagnosis of FXIII deficiency was as per patients' medical records which also included underlying gene defect if known (FXIII subunit A, FXIII subunit B, other). Other available genotyping information was collected.

9.3.2 Exclusion criteria

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

9.3.2.1 Withdrawal criteria

There were 3 withdrawal criteria:

- The patient may withdraw at will at any time (Withdrawal criterion 1: W1).
- The patient's parent or patient's LAR may withdraw the patient at any time (Withdrawal criterion 2: W2).
- Patient may be withdrawn from the study at the discretion of the physician or the sponsor due to safety concern if medically justified or if judged non-compliant with study procedures[a] (Withdrawal criterion 3: W3)

[a] This withdrawal criteria was removed in a protocol amendment no.4 dated 11 August 2014.

9.3.3 Sources of patients

The study included patients exposed to rFXIII in the EU, and additional patients from selected non-EU countries including Canada and the US. In addition, contractual collaboration with the PRO-RBDD was established to collect data on patients with congenital FXIII A-subunit deficiency. Patients participating in registries other than PRO-RBDD would be identified in the case report form (CRF).

9.3.4 Methods of selection of patients

Patients were identified by investigators and included in the study based on inclusion criteria, see Section 9.3.1.

9.4 Variables

The study was designed to observe the use of rFXIII in normal clinical practice and hereby further explore the safety profile and effectiveness of rFXIII. The safety profile of rFXIII was monitored via collection of data on ADRs comprising FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of effect. Also, all SAEs, medical events of special interest and medication errors and near medication errors were collected. The effectiveness of prophylactic treatment with rFXIII in patients with congenital FXIII A-subunit deficiency was measured by collecting data on ABR. Also, data on treatment with rFXIII for other uses than prophylactic treatment in patients with congenital FXIII A-subunit deficiency was collected.

9.5 Data sources and measurement

It was the intention of this non-interventional study to observe routine treatment of the individual patient. Data and results available in the patient's medical record, in the patient diary and from assessments and laboratory sampling (performed according to clinical practice at the participating sites) were recorded in the paper case report form. Information related to treatment and bleeding episodes were captured in a patient diary by the patient or parent/caregiver. In case a patient was unable to enter a treatment in the diary, or was hospitalised, it was to be reported in the patient record and subsequently in the paper case report form by the physician.

Novo Nordisk A/S provided the CRFs. CRF entries were to be printed legibly using a ballpoint pen. It was to be ensured that all questions were answered and that no empty data blocks existed. It was to be ensured that no information was recorded outside the data blocks. If a test/assessment had not been done and would not be available, this was to be indicated by writing "ND" (not done) in the respective answer field in the CRF. If the question was irrelevant (e.g., was not applicable) it was to be indicated by writing "NA" (not applicable) in the respective answer field. Further guidance could be obtained from the instruction in the CRF. By signing the affirmation statement, the physician confirmed that the information was complete and correct.

In addition to the above, this report also includes data collected and reported in contractual collaboration with the PRO-RBDD registry.

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 incorrectness of dose and bleeding evaluation; this was minimised by review of the diary by the physician before entering into the CRF. To minimise misclassification, the patient and the physician evaluated the bleeding episodes together at the next visit. Medical consistency checks by qualified medical persons to capture and resolve inconsistencies was performed.

9.7 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 enforced to protect the identity of human patients in all presentations and publications as required by local/regional/national requirements. Appropriate measure such as encryption of data files was 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 source data. In cases where laboratory data was transferred via non-secure electronic networks, data was encrypted during transfer.

9.8 Statistical methods

This was a purely descriptive study and the statistical analyses and presentations did not include any testing of pre-specified hypotheses. All analyses and presentations were based on the full analysis set. The full analysis set comprised all the patients who had entered the study fulfilling the inclusion and exclusion criteria and had received at least one dose administration of rFXIII in the study period. The full analysis set was identical to the safety analysis set. This report includes all the statistical descriptions listed below. For adverse events rates and bleeding rates, lost-to-follow-up was accounted for by using the time spent in study as the denominator.

9.8.1 Main summary measures

Mean (standard deviation), median (min – max) and ABR (95% confidence interval (CI)) were used to summarise data.

9.8.2 Main statistical methods

Primary endpoints

The specific ADRs of the primary endpoint (anti-FXIII antibodies, allergic reaction, embolic and thrombotic events and lack of therapeutic effect) were summarised, displaying the number of reactions and the number and percentage of patients experiencing the reaction relevant within system organ class (SOC) and Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT). The endpoint was presented for all patients as well as by special populations, comprising children, elderly, pregnant and lactating women, and patients with renal insufficiency.

All the specific ADRs were further listed with patient ID, site, age, PT, date of first dose, date of onset, date of arrest, severity, if it was serious or not, relationship to study drug, action, and outcome.

Secondary endpoints

The secondary endpoints covered the following five types of assessments:

- All serious adverse events
- All medical events of special interest
- All medication errors and near medication errors
- Use of rFXIII other than for prophylactic treatment.
- ABR

The first 3 secondary endpoints were presented for all patients as well as by special populations, comprising children, elderly, pregnant and lactating women, and patients with renal insufficiency.

All the secondary endpoints were collected from the first study-related activity after signing the informed consent to the end of patient's participation in the study, expected to last a maximum of 6 years.

Dates for signing informed consent forms and visit dates are listed by patient in Annex 16.2.4, Listings 16.2.4.1 and 16.2.4.2, respectively.

Serious adverse events

Serious adverse events (SAEs) were summarised, displaying the number of events and the number and percentage of patients experiencing the event by MedDRA PT.

SAEs were further listed with patient ID, age, PT, date of onset, date of arrest, severity, if it was serious or not, relationship to study drug, action, and outcome.

Medical events of special interest

Medical events of special interest were summarised, displaying the number of events and the number and percentage of patients experiencing the reaction by MedDRA PT. The following were defined as medical events of special interest in this study:

- Medication errors and near medication errors including administration of wrong drug, wrong route of administration, administration of a high dose with the intention to cause harm or an accidental overdose. Any errors of reconstitution procedure or storage of the reconstituted product also are considered to be medication errors
- Suspected transmission of an infectious agent via the study product
- Anti-FXIII antibodies
- Allergic reactions
- Embolic or thrombotic events
- Lack of therapeutic effect

Medical events of special interest were further listed by patient ID, age, PT, date of onset, date of arrest, severity, and seriousness, relationship to study drug, action, and outcome.

Medication errors and near medication errors

Medication errors and near medication errors constituted a specific subset of medical events of special interest. They were summarised, displaying the number of medication errors and the number and percentage of patients experiencing the reaction by MedDRA PT.

Medication errors and near medication errors were further listed by patient ID, site, age, PT, date of first dose, date of onset, date of arrest, severity, if it was serious or not, relationship to study drug, action, and outcome.

Use of rFXIII other than for prophylactic treatment

The use of rFXIII in patients with congenital FXIII A subunit deficiency, other than for prophylactic treatment included on demand treatment (patients who do not receive regular treatment but are only treated when needed). This also included an additional product dosage for patients on prophylactic treatment to treat breakthrough bleeds in relation to traumas, surgeries, and spontaneous bleeds referred to as “treatment of bleeds”. The use of rFXIII for other than prophylaxis was listed by patient ID, age and treatment.

Annualised Bleeding rate

The ABR (covering both treatment-requiring and non treatment-requiring) was calculated from the bleeding episodes which occurred from the first study-related activity after signing the informed consent to the end of patient’s participation in the study.

The treatment-requiring bleeding episodes described in this study report are the bleeding episodes requiring treatment with a FXIII containing product like rFXIII and Fibrogammin.

ABR was summarised by cause (spontaneous, traumatic and surgery), therapeutic regimen (prophylactic therapy, on-demand therapy, surgery), severity, site of bleeding, haemostatic treatment administered (product name) and haemostatic response. The ratio between traumatic and

spontaneous bleeding rates was further summarised and listed and graphical displays of the bleeding rates and the referred ratio are presented by patient, ranking the patients according to increased values.

Bleeding episodes were further listed, including information about cause, severity, location, date and time of onset, date and time of arrest, product name, dose, haemostatic response, related concomitant illness and related concomitant medication.

Definition of haemostatic response:

- Excellent: abrupt pain relief and/or substantial improvement in signs of bleeding within approximately 8 hours after a single infusion.
- Good/Effective: some pain relief and/or improvement in signs of bleeding within approximately 8 hours after infusion of product, but not requiring more than one infusion for complete bleeding arrest.
- Moderate/partly effective: slight beneficial effect on pain relief and/or minimal improvement in signs of bleeding within approximately 8 hours after the first product infusion, but not requiring more than one infusion for complete bleeding arrest.
- None: no improvement or worsening of symptoms or use of other FXIII products.

9.8.3 Missing values

Since the primary and all the secondary endpoints were event driven endpoints, it was assumed that all relevant events for each endpoint have been reported.

9.8.4 Sensitivity analyses

No sensitivity analyses were performed.

9.8.5 Amendments to the statistical analysis plan

There were no changes made to the statistical analysis plan.

9.9 Quality control

During the course of the study, the monitor visited the study site at intervals. The purpose of these visits was to ensure that the CRFs were completed correctly, the protocol was adhered to, and to collect completed CRF pages. Data for at least 20% of the enrolled patients was source data verified.

10 Results

10.1 Participants

A total of 30 patients were enrolled and exposed to rFXIII in this study. There were no screening failures (Annex 16.2.1, Listing 16.2.1.1). The patient disposition is presented in Table 10-1.

Of the 30 patients, 5 patients were withdrawn from the study and 25 patients completed the study. The criteria for completing the study was minimum of 2 years participation or 24 exposure days (whichever came first, unless the patient had dropped out). The reasons for withdrawal were as follows:

- A [redacted] patient was withdrawn by the investigator after having received [redacted] prophylactic dose of rFXIII and a [redacted] dose due to a [redacted] bleeding episode. The investigator withdrew the patient as the patient was noncompliant with the study procedures which is related to W3 (according to W3, the patient may be withdrawn from the study at the discretion of the physician or the sponsor due to a safety concern if medically justified or if judged non-compliant with study procedures). However, this withdrawal criterion was later removed from the list of withdrawal criteria in a protocol amendment.
- Two patients withdrew due to W1 which is withdrawal by patient at will at any time.
- Two patients withdrew due to 'other' reasons (one of these patients withdrew for personal reasons and the [redacted]

No patients had major surgery during the study. No pregnant and lactating women or patients with renal insufficiency were enrolled in this study. Consequently, no results are presented for these two special populations.

The withdrawn patients are listed in Annex 16.2.1, Listing 16.2.1.2. Informed consent details for individual patients is listed in Annex 16.2.4, Listing 16.2.4.1.

Table 10-1 Patient disposition – summary – full analysis set

	Children < 18 years	Adults (18 - 65 years)	Elderly > 65 years	Total
Screened	13	15	2	30
Exposed	13(100.0)	15(100.0)	2(100.0)	30(100.0)
Withdrawal	1(7.7)	3(20.0)	1(50.0)	5(16.7)
Withdrawal Criteria:W1	1(7.7)	1(6.7)	0(0.0)	2(6.7)
Withdrawal Criteria:W3	0(0.0)	0(0.0)	1(50.0)	1(3.3)
Other	0(0.0)	2(13.3)	0(0.0)	2(6.7)
Completed study	12(92.3)	12(80.0)	1(50.0)	25(83.3)
Full analysis set	13(100.0)	15(100.0)	2(100.0)	30(100.0)
Safety analysis set	13(100.0)	15(100.0)	2(100.0)	30(100.0)
Years in study	37.0	34.4	3.9	75.3
EDs in study	431	404	53	888
Undergone minor surgery*	3(23.1)	3(20.0)	0(0.0)	6(20.0)
Undergone major surgery**	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Patients with renal insufficiency	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Pregnant or lactating women	0(0.0)	0(0.0)	0(0.0)	0(0.0)

N: Number of patients, %: Percentage of exposed patients, * Minor surgery during study
** Major surgery during study
The full analysis set and the safety analysis set both consists of all patients exposed to rFXIII.
ED: Exposure days

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Cross-reference: EOT Table 14.2.1

Protocol deviations

A total of 22 important protocol deviations (PDs) were reported in this study as of the database lock date of 10 July 2019. This included 1 study-level PD, 2 site-level PDs and 19 patient-level PDs

The study level PD belonged to the category ‘other’ and related to post-study follow-up period or post-treatment follow-up period defined in the protocol. This being a non-interventional study, patients with FXIII deficiency would continue treatment with rFXIII after end of study, thus a follow-up period was not applicable. This was corrected by distributing a newsletter to the sites informing about the decision to end safety data collection at end of study visit (visit 3).

There were 2 site-level PDs reported in this study. One PD belonged to the category ‘informed consent’ and related to the ICF process not adequately recorded in source documents. This was corrected by updating the source documents. One PD belonged to the category ‘other’ and related to blood samples (FXIII activity and anti-rFXIII antibodies) collected inconsistently and not according to protocol for 3 patients at one of the sites.

Among the 19 patient-level PDs, 1 PD was related to 'SAE notification/safety procedure', 7 PDs were related to 'informed consent' and 11 PDs were in 'other' category. Please refer to Annex 16.2.2 Listing 16.2.2.1 to 16.2.2.10 for more details on important PDs.

10.2 Descriptive data

The mean age of the patients was 25.5 years, and there were slightly more males (17, 57%) than females (13, 43%). The majority (22, 73%) of the patients were White. The race for 3 patients was reported as 'other' ([redacted]

There were 3 patients from Canada, 4 patients from Denmark, 1 patient from Hungary, 5 patients from Italy, 3 patients from Spain, 1 patient from United Kingdom and 13 patients from United States of America.

The patient demographics and baseline characteristics are presented in the Table 10-2 and listed by patient in Annex 16.2.4, Listing 16.2.4.3. The body measurements at baseline are presented in EOT Table 14.1.2.

Table 10-2 Baseline demographics – full analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Age at baseline (years)				
N	13	15	[redacted]	30
Mean (SD)	9.2 (4.9)	33.9 (11.9)		25.5 (18.8)
Median	9.0	33.0		21.0
Min ; Max	[redacted]			
Gender, N (%)				
N	13 (100.0)	15 (100.0)	2 (100.0)	30 (100.0)
Male	[redacted]			17 (56.7)
Female				13 (43.3)
Country, N (%)				
N	13 (100.0)	15 (100.0)	2 (100.0)	30 (100.0)
Canada	[redacted]			3 (10.0)
Denmark				4 (13.3)
Hungary				1 (3.3)
Italy				5 (16.7)
Spain				3 (10.0)
United Kingdom				1 (3.3)
United States of America				13 (43.3)
Ethnicity, N (%)				
N	13 (100.0)	15 (100.0)	2 (100.0)	30 (100.0)
Hispanic or Latino	[redacted]			6 (20.0)
Not Hispanic or Latino				22 (73.3)
NA				2 (6.7)
Race, N (%)				
N	13 (100.0)	15 (100.0)	2 (100.0)	30 (100.0)
Black Or African American	[redacted]			4 (13.3)
White				22 (73.3)
Other				3 (10.0)
NA				1 (3.3)

N: Number of patients, %: Percentage of patients, SD: Standard deviation, NA: not applicable
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Cross-reference: EOT Table 14.1.1

Concomitant medications and illness/medical history at baseline

A total of 29 patients reported taking concomitant medications. The details on concomitant medications are presented in EOT Table 14.1.3. Concomitant medications by patient are listed in Annex 16.2.4, Listing 16.2.4.7.

A total of 17 patients reported concomitant illness/medical history at baseline. The details are provided in EOT Table 14.1.4 and Annex 16.2.4, Listing 16.2.4.8.

Before entry into the study, 6 patients had allergic reactions to pharmaceutical drug and 2 patients had a history of embolic and/or thrombotic events (EOT Table 14.1.5 and Annex 16.2.4, Listing 16.2.4.9). For 2 patients, elective surgery (minor) was performed within the last 12 months before entry in the study (Annex 16.2.4, Listing 16.2.4.10).

Before entry into the study, a total of 25 patients were on prophylaxis, 1 patient was on-demand and 4 patients were on supplemental on-demand treatment (2 patients receiving additional doses of rFXIII while on prophylaxis and 2 patients receiving plasma derived FXIII products while on prophylaxis). For patients on prophylaxis, within the last 24 months prior to entry into the study, the mean of the number of bleeding episodes for treatment-requiring bleeds was 0.17 and for non treatment-requiring bleeds was 1.00. In the patient requiring on-demand treatment, neither treatment-requiring nor non treatment-requiring bleeding episodes were reported within the last 24 months prior to entry into the study. The treatment history of the full analysis set is presented in EOT Table 14.1.11. Bleeding treatment history before entry in study is listed for patients on prophylaxis regimen and those on non-prophylaxis regimen in Annex 16.2.4, Listings 16.2.4.5 and 16.2.4.6, respectively.

A total of 11 patients participated in different haemophilia registries (EOT Table 14.1.10). These registries included:

- The American Thrombosis and Haemostasis Network (ATHN) dataset: [redacted] patients
- Canadian Haemophilia society of rare bleeding disorders: [redacted] patient
- The Canadian Bleeding Disorders Registry (CBDR): [redacted] patient
- The Centers for Disease Control and Prevention (CDC) surveillance: [redacted] patients
- Community counts rare coagulation disorders: [redacted] patient
- European Haemophilia Safety Surveillance (EUHASS): [redacted] patients
- EUHASS, National Haemophilia Database (NHD): [redacted] patient

[redacted]

[redacted]

Haemophilia history is listed by patients in Annex 16.2.4, Listing 16.2.4.4.

Of the 30 patients who were dosed with rFXIII, the genotype information was available for 27 patients. [redacted] (EOT Table 14.1.8). Genotype characteristics of individual patients are listed in Annex 16.2.4, Listing 16.2.4.11.

The mean of the total number of doses per patient was 29.6 [standard deviation (SD): 16.8] (EOT Table 14.2.3). The date, time and the actual dose administered by patient are listed in Annex 16.2.5, Listing 16.2.5.1.

No patients were excluded from the full analysis set, Annex 16.2.3, Listing 16.2.3.1.

Visit details for individual patients is listed in Annex 16.2.4, Listing 16.2.4.2.

10.3 Outcome data

The section is not applicable for this study.

10.4 Main results

10.4.1 Primary endpoint

The primary endpoint was the incidence of specific ADRs in patients with congenital FXIII A-subunit deficiency treated with rFXIII, comprising anti-FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of effect, collected during a study period of up to 6 years; please refer to Section 10.6 for safety related results.

10.4.2 Secondary endpoints

The secondary endpoints included both safety and effectiveness endpoints; for safety related secondary endpoints, please refer to Section 10.6. Effectiveness related endpoints are discussed in this section.

10.4.2.1 Use of rFXIII other than for prophylactic treatment

All the 30 patients in the study were on prophylactic treatment. Please refer to Section 9.8.2 for definition of "use of rFXIII other than prophylactic treatment" and for definition of haemostatic response.

A total of 5 traumatic bleeding episodes in 4 patients were treated with an additional dose of rFXIII in the study (refer to Annex 16.2.5, Listing 16.2.5.2 for additional details). All the patients showed a good to excellent haemostatic response.

- A [redacted] patient had bleeding on the [redacted] days after the last prophylactic dose. [redacted] was treated with [redacted] IU/kg of rFXIII on [redacted] and showed a good haemostatic response. The FXIII activity recorded on [redacted] prior to the bleeding episode was [redacted] IU/mL.
- A [redacted] patient [redacted] and had a [redacted] injury, [redacted] days after the last prophylactic dose. [redacted] was treated with [redacted] IU/kg of rFXIII on [redacted] and showed an excellent haemostatic response. The FXIII activity recorded on [redacted], prior to the bleeding episode was [redacted] IU/mL.
- A [redacted] patient had bleeding when [redacted] days after the last prophylactic dose. [redacted] was treated with [redacted] IU/kg of rFXIII on [redacted] and showed an excellent haemostatic response. The FXIII activity recorded on [redacted] prior to the bleeding episode was [redacted] IU/mL.
  - The same patient experienced [redacted], [redacted] days after the last prophylactic dose. [redacted] was treated with [redacted] IU/kg of rFXIII on [redacted] and showed an excellent haemostatic response. The FXIII activity recorded on [redacted] prior to the bleeding episode was [redacted] IU/mL.
- A [redacted] received a prophylactic dose of rFXIII and underwent [redacted] After [redacted] days of this prophylactic dose, the patient [redacted]

[redacted] and had [redacted] to [redacted] The patient's [redacted] was treated with [redacted] IU/kg of rFXIII and had an excellent haemostatic response.

10.4.2.2 Annualised bleeding rate

A total of 65 bleeding episodes were reported by 14 patients in the study. Of these, 6 bleeding episodes required treatment with a FXIII containing product. Of these, a total of 5 traumatic bleeding episodes were treated with an additional dose of rFXIII with good to excellent haemostatic response (see Section 10.4.2.1 for more details). The [redacted] traumatic bleed was reported by a [redacted] patient when the patient [redacted] and was treated with [redacted]

The overall estimated ABR for treatment-requiring bleeding episode was 0.066 bleeds/patient/year with a 95% CI of [0.029; 0.150]. The overall estimated ABR of all bleeding episodes was 0.850 bleeds/patient/year with a 95% CI of [0.246; 2.940] (Table 10-3). The mean duration of bleeds was 32.1 hours (SD: 48.0) (EOT Table 14.2.6).

There were no spontaneous treatment-requiring bleeding episodes.

A total of 59 non treatment-requiring bleeding episodes were reported in this study, of which 41 bleeds were reported by a [redacted]-year-old [redacted] who repeatedly had [redacted] bleeds.

A total of 16 (53%) patients had no bleeding episodes during the entire study duration. A total of 25 patients (83%) had no treatment-requiring bleeding episodes during the entire study duration.

The ABR by site of bleed was estimated for haemarthrosis bleeding episode (0.013 bleeds/patient/year), muscular bleeding episode (0.013 bleeds/patient/year), subcutaneous bleeding episodes (0.093 bleeds/patient/year) and other bleeding episodes (0.731 bleeds/patient/year). Refer to EOT Table 14.2.11 for more details.

The ABR by age was estimated as follows:

- children (<18 years):1.596 bleeds/patient/year
- adult (18 to 65 years): 0.145 bleeds/patient/year
- elderly (>65 years): 0.256 bleeds/patient/year

Refer to EOT Table 14.2.14 for more details.

The ABR by cause of bleeding and bleeding severity is presented in EOT Tables 14.2.9 and 14.2.10, respectively. The ABR by haemostatic response is presented in EOT Table 14.2.13. The ABR of bleeding episodes by haemostatic treatment administered and for previously rFXIII untreated patients is presented in EOT Tables 14.2.12 and 14.2.15, respectively.

Table 10-3 Annualised bleeding rate of all bleeding episodes – full analysis set

	Treatment requiring	Non Treatment requiring	All
Number of patients	30	30	30
Number of patients with bleed	5	10	14
Total number of bleeds	6	59	65
Range of bleedings	0 ; 2	0 ; 41	0 ; 41
Mean bleedings per patient	0.200	1.967	2.167
Mean observation period (days)	916.5	916.5	916.5
Total observation period (years)	75.3	75.3	75.3
Poisson analysis*			
Annualised bleeding rate	0.066	0.784	0.850
95% CI	0.029 ; 0.150	0.204 ; 3.011	0.246 ; 2.940
Cause of bleed			
N	6	50**	56
Spontaneous	-	30	30
Traumatic	6	18	24
Not known	-	2	2
Haemostatic response			
N	6	-	6
Excellent	4	-	4
Good	2	-	2

* A 95% CI for the annualised bleeding rate is estimated from a Poisson analysis with over-dispersion if the number of bleeds is greater than 1, otherwise only the Poisson estimate is provided assuming no over-dispersion
** The cause of bleed for 9 non-treatment requiring episodes was missing in the CRF.

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Cross-reference: Modified from EOT Tables 14.2.4 and 14.2.8

A total of 58 bleeding episodes were reported in 12 patients during home treatment. Of these, 5 bleeds were treatment-requiring, all of which were traumatic, and severity was reported as mild/moderate (see EOT Table 14.2.5 for more details).

The individual patient listing of non treatment-requiring bleeding episodes, treatment-requiring bleeding episodes, and all bleeding episodes is presented in Annex 16.2.6, Listing 16.2.6.1 to Listing 16.2.6.3, respectively.

When judged necessary by the treating physician, samples for evaluating FXIII activity were collected. The mean FXIII activity of the pre-dose samples (troughs) was 0.11 IU/mL (SD: 0.08) (derived from Annex 16.2.8, Listings 16.2.8.1).

The FXIII activity assay used at the central laboratory was the Berichrom assay. FXIII activity by visit, analysed at the central laboratory is presented in EOT Table 14.3.5.1 and analysed at the local laboratory is presented in EOT Table 14.3.5.2 (listed by patient in Annex 16.2.8, Listings 16.2.8.1 and 16.2.8.2, respectively).

Laboratory reference range for rFXIII activity is presented in EOT Table 14.3.4.1 and limits of quantification are presented in EOT Table 14.3.4.2. FXIII activity outside reference range is listed in EOT Table 14.3.4.4.

10.4.2.3 Surgery

A total of 6 patients underwent 9 minor surgeries during the study (Table 10-4, EOT Table 14.2.7 and Annex 16.2.6, Listing 16.2.6.5). Out of these, 5 patients had minor surgeries, 0-3 days after the last prophylactic dose. One patient had [redacted] minor surgeries, [redacted] and [redacted] days after the last prophylactic dose and received an extra vial of rFXIII ([redacted] IU) prior to both the surgeries: [redacted] IU/kg for the first surgery and [redacted] IU/kg for the second surgery.[3]

The haemostatic response during and after the surgeries was good to excellent (the haemostatic response was missing for one surgery). There were no major surgeries during the study.

Table 10-4 Details of surgery

Age	Sex (F/M)	Surgery	Time since last prophylaxis	Treatment prior surgery	Treatment post-surgery*	Outcome**
[redacted]						

*Post-surgery is defined the time period from 1-10 days after surgery.

**Haemostatic response after surgery

Source: Modified from EOT Table 14.2.7 and Annex 16.2.6, Listing 16.2.6.5

10.4.3 Summary of main results

Secondary effectiveness endpoints:

Use of rFXIII other than for prophylactic treatment

- A total of 5 traumatic bleeding episodes were treated with an additional dose of rFXIII in the study. All the patients showed a good to excellent haemostatic response.

Annualised bleeding rate

- The overall estimated ABR for treatment-requiring bleeding episode was 0.066 bleeds/patient/year.
- There were no spontaneous treatment-requiring bleeding episodes.
- The overall estimated ABR of all bleeding episodes was 0.850 bleeds/patient/year.

10.5 Other analyses

The section is not applicable for this report.

10.6 Adverse events and adverse drug reactions

Extent of exposure

The consumption of rFXIII are summarised in Table 10-5. The consumption of rFXIII used for the treatment (including all doses given for prophylaxis and treatment of bleed) per year per patient was 395.9 IU/kg/year (SD: 155.23) and the average rFXIII dose given for prophylaxis was 37.2 IU/kg (SD: 12.16). The exposure of rFXIII is summarised in EOT Table 14.2.3.

Table 10-5 Consumption of rFXIII during the study - full analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Consumption used for treatment* per year per patient** (IU/kg/year)				
N	13	15	2	30
Mean (SD)	470.2 (195.79)	337.8 (89.41)	349.1 (3.24)	395.9 (155.23)
Median	452.5	348.4	349.1	404.1
Min ; Max	154.2 ; 982.3	173.7 ; 456.6	346.8 ; 351.4	154.2 ; 982.3
Average prophylaxis dose*** (IU/kg)				
N	420	364	53	837
Mean (SD)	43.7 (12.57)	31.3 (7.71)	26.9 (0.84)	37.2 (12.16)
Median	38.9	31.2	26.7	35.7
Min ; Max	30.3 ; 89.7	18.2 ; 50.7	26.0 ; 28.7	18.2 ; 89.7
Average dose for treatment of bleed from start to stop of bleed+ (IU/kg/bleed)				
N	4	1	0	5
Mean (SD)	42.2 (7.73)	36.0 (-)	- (-)	41.0 (7.24)
Median	39.6	36.0	-	37.6
Min ; Max	36.3 ; 53.3	36.0 ; 36.0	- ; -	36.0 ; 53.3

*Consumption used for treatment includes all doses given (prophylaxis, treatment of bleed)
The contribution from the last prophylactic dose given is adjusted to the remaining relative part of planned dosing interval of 28 days up to the cut-off date
**N is number of patients
***N is number of doses
+N is number of bleeds

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Cross-reference:EOT Table 14.2.2

10.6.1 Primary endpoint: specific adverse drug reactions

The specific ADRs of the primary endpoint are anti-FXIII antibodies, allergic reaction, embolic and thrombotic events and lack of therapeutic effect.

A total of 3 specific ADRs in 2 patients were reported in this study; 2 incidences of positive non-neutralising anti-rFXIII antibody in one patient at 2 time-points ([redacted]) and a suspected lack of therapeutic effect in another patient (Table 10-6 and EOT Table 14.3.1.4).

There were no allergic reactions and no embolic and thrombotic events assessed as related to rFXIII reported in this study.

Table 10-6 Specific adverse drug reactions – safety analysis set

	Children < 18 years N (%) E [R]	Adults (18 - 65 years) N (%) E [R]	Elderly > 65 years N (%) E [R]	Total N (%) E [R]
Number of patients	13	15	2	30
Total time in study (years)	37.00	34.44	3.92	75.36
Total number of exposure days	431	404	53	888
Any specific adverse drug reactions	[redacted]			
Specific adverse drug reaction				
Anti-FXIII antibody				
Lack of therapeutic effect				

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

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Cross-reference: EOT Table 14.3.1.2

The incidence of non-neutralising anti-rFXIII antibody concerned a [redacted] patient who tested positive at the [redacted] visit of mentor™6 after having participated in the NN1841-3760 (mentor™4) and NN1841-3835 (mentor™5) for a total period of [redacted] years. The patient was in mentor™4 from [redacted] until [redacted] and then continued in mentor™ 5 from [redacted] to [redacted] The patient was treated with [redacted] after [redacted] and was included in NN1841-3868 (mentor™6) on [redacted]

The first sample positive for low-titre non-neutralising anti-rFXIII antibodies was from [redacted], and the second positive sample with lower titre than the first for binding antibodies was from [redacted] all the anti-rFXIII neutralising antibody tests were negative. Thereafter, the samples have been negative for binding antibodies ([redacted] and [redacted] The patient thus developed low-titre transient non-neutralising anti-rFXIII antibodies after several years of treatment with NovoThirteen®. No clinical findings were associated with these antibodies and there was no evidence of lack of effect.

The event of suspected lack of therapeutic effect concerned a [redacted]. The patient was on rFXIII since [redacted] The patient repeatedly had [redacted] bleeds which occurred when [redacted]. The patient had received the prophylactic dose on [redacted]. On [redacted], the investigator reported decreased therapeutic response. The FXIII activity recorded on [redacted] was [redacted] IU/mL. The next prophylactic dose was on [redacted]. Since FXIII activity was [redacted] IU/mL on [redacted], the FXIII activity would be > [redacted] IU/mL on [redacted] when the investigator reported the suspected lack of therapeutic response. Hence, the patient had normal FXIII in-vitro activity levels and also had no anti-rFXIII antibodies. The patient [redacted] from the event of suspected lack of therapeutic effect on [redacted].

None of the patients withdrew from the study due to lack of efficacy of the rFXIII product (Annex 16.2.6, Listing 16.2.6.4).

There were no neutralising antibodies reported during the study period, refer to EOT Table 14.3.5.5 (Annex 16.2.8, Listing 16.2.8.5).

There were no patients with renal insufficiency and there were no pregnant or lactating women in this study.

There were no ADRs in previously rFXIII untreated patients (EOT Table 14.3.1.3). Anti rFXIII antibodies are presented by visits in EOT Table 14.3.5.3 (listed by patient in Annex 16.2.8, Listing 16.2.8.3) and by titre in EOT Table 14.3.5.4 (listed by patient in Annex 16.2.8, Listing 16.2.8.4).

No individual FXIII activity or antibody assessments were excluded from analysis, Annex 16.2.8, Listing 16.2.8.6 to 16.2.8.10.

10.6.2 Adverse events

A total of 18 patients had 44 adverse events (60.0%) (Table 10-7). The 44 adverse events were mainly within the MedDRA SOCs of "Infections and infestations" (11 events reported in 7 patients, PTs included nasopharyngitis, sepsis, conjunctivitis, gastroenteritis viral, influenza, sialoadenitis, tonsillitis and upper respiratory tract infection), "Nervous system disorders" (7 events reported in 4 patients, PTs included dizziness, post-traumatic headache, dysarthria and headache), "General disorders and administration site conditions" (6 events reported in 4 patients, PTs included chest discomfort, fatigue, influenza like illness and therapeutic response decreased), and "Injury, poisoning and procedural complications" (5 events reported in 4 patients, PTs included contusion, accidental overdose, ligament sprain and limb injury), please see, EOT Table 14.3.1.5 and Annex 16.2.7, Listing 16.2.7.1.

Adverse events with possible or probable relation to study product

A total of 11 events reported by 7 patients (23.3%) (distributed over different SOCs) were evaluated to be possibly or probably related to the rFXIII by the investigator (Table 10-8, EOT Table 14.3.1.6 and Annex 16.2.7, Listing 16.2.7.4). None of these events were SAE and the patients recovered from all the events (EOT Table 14.3.1.12).

- A [redacted] patient reported headache of mild severity on [redacted]. The event was possibly related to rFXIII. The patient [redacted] from the event on [redacted].
- A [redacted] patient reported 3 events of chest discomfort. Refer to Section 10.6.3.1 for more details.
- A [redacted] patient reported dizziness and fatigue on [redacted]. Both the events were mild in severity and possibly related to rFXIII. The patient [redacted] from dizziness on [redacted] and from fatigue on [redacted].
- A [redacted] patient reported an event of dizziness on [redacted]. The event was mild in severity and possibly related to rFXIII. The patient [redacted] from the event on the [redacted].
- A [redacted] tested positive for non-neutralising anti-rFXIII antibodies on [redacted] and [redacted].Refer to Section 10.6.1 for more details.
- A [redacted] reported therapeutic response decreased (suspected lack of therapeutic effect) on [redacted]. Refer to Section 10.6.1 for more details.
- A [redacted] patient reported thrombophlebitis superficial on [redacted]. Refer to Section 10.6.3.1 for more details.

There were no non-treatment emergent AEs in this study (EOT Table 14.3.1.18, Annex 16.2.7, Listing 16.2.7.2).

There was 1 severe AE of sepsis reported (refer to Section 10.6.3.1 Case ID [redacted] for more details). A total of 13 moderate AEs were reported in 10 patients (33.3%) and 30 mild AEs in 13 patients (43.3%). Please see EOT Table 14.3.1.7, 14.3.1.8 and EOT Table 14.3.1.9, respectively.

None of the patients were withdrawn from the study due to AEs, see EOT Table 14.3.2.2.

Table 10-7 Overview of adverse events – safety analysis set

	Children < 18 years N (%) E [R]	Adults (18 - 65 years) N (%) E [R]	Elderly > 65 years N (%) E [R]	Total N (%) E [R]
Number of patients	13	15	2	30
Total time in study (years)	37.00	34.44	3.92	75.36
Total number of exposure days	431	404	53	888
All adverse events	9 (69.2) 16 [0.43]	7 (46.7) 23 [0.67]	2 (100.0) 5 [1.28]	18 (60.0) 44 [0.58]
Serious adverse events	2 (15.4) 2 [0.05]	4 (26.7) 7 [0.20]	1 (50.0) 1 [0.26]	7 (23.3) 10 [0.13]
Adverse events by severity				
Mild	7 (53.8) 12 [0.32]	5 (33.3) 16 [0.46]	1 (50.0) 2 [0.51]	13 (43.3) 30 [0.40]
Moderate	3 (23.1) 4 [0.11]	5 (33.3) 6 [0.17]	2 (100.0) 3 [0.77]	10 (33.3) 13 [0.17]
Severe	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Adverse events by relationship				
Probably or possibly related	2 (15.4) 3 [0.08]	3 (20.0) 5 [0.15]	2 (100.0) 3 [0.77]	7 (23.3) 11 [0.15]
Unlikely related	7 (53.8) 13 [0.35]	6 (40.0) 18 [0.52]	2 (100.0) 2 [0.51]	15 (50.0) 33 [0.44]
Adverse events				
Leading to withdrawal	-	-	-	-

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

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Cross-reference: EOT Table 14.3.1.1.

Table 10-8 Adverse events with possible or probable relation to study product

Age	Sex (M/F)	Event	Severity	Causality	Outcome
[redacted]		Headache	Mild	[redacted]	
		Chest discomfort	Mild		
		Chest discomfort	Mild		
		Chest discomfort	Moderate		
		Dizziness	Mild		
		Fatigue	Mild		
		Dizziness	Mild		
		Non-neutralising antibodies positive	Mild		
		Pain in extremity	Mild		
		Therapeutic response decreased*	Mild		
		Thrombophlebitis superficial**	Moderate		

No events with possible or probable relation to study product were serious adverse event.

* Assessed by investigator as suspected lack of therapeutic response.

** As per the protocol, superficial thrombophlebitis is not considered as an embolic and thrombotic event.

Source: Modified from EOT Table 14.3.1.6 and Annex 16.2.7, Listing 16.2.7.4

10.6.3 Secondary safety endpoints

10.6.3.1 All serious adverse events

A total of 10 SAEs were reported in 7 patients, see Table 10-9.

Table 10-9 Serious adverse events

Case number	Age (years)	Sex (F/M)	Preferred Term	Severity	Causality	Outcome
[redacted]			Haemarthrosis	Moderate	[redacted]	
			Ovarian rupture	Moderate		
			Post-traumatic headache	Moderate		
			Dizziness	Mild		
			Influenza	Moderate		
			Deep vein thrombosis*	Mild		
			Sialoadenitis	Moderate		
			Sepsis	Moderate		
			Sepsis	Severe		

Case number	Age (years)	Sex (F/M)	Preferred Term	Severity	Causality	Outcome
[redacted]			Arthralgia	Moderate	[redacted]	

*Assessed by investigator as caused by peripheral vein catheter

Source: Modified from EOT Tables 14.3.1.10, 14.3.2.1 and Section 14.3.3

A brief summary of the SAEs is provided below:

[redacted]

[redacted]

Please see Section 14.3.3, EOT Tables 14.3.1.8, 14.3.1.9 and 14.3.2.1 for more details.

10.6.3.2 Medical events of special interest

There were 4 medical events of special interest reported in this study, see Table 10-10, EOT Table 14.3.1.13 and Annex 16.2.7, Listing 16.2.7.6.

Table 10-10 Medical events of special interest

Case number	Age	Sex (F/M)	Preferred term	Severity	Causality	Outcome
[redacted]			Deep vein thrombosis*	Mild	[redacted]	
			Non-neutralising antibodies positive	Mild		
			Therapeutic response decreased**	Mild		
			Accidental overdose***	Mild		

* Assessed by investigator as caused by peripheral vein catheter.
** Assessed by investigator as suspected lack of therapeutic response.
*** Assessed by investigator as Medication error due to rFXIII overdose.

Source: Modified from EOT Tables 14.3.1.13 and Annex 16.2.7, Listing 16.2.7.6

A brief summary of the medical events of special interest is provided below:

- [redacted]

10.6.3.3 All medication errors and near medication errors

There was one case of accidental overdose reported and was classified as medication error, refer to Section 10.6.3.2, EOT Table 14.3.1.16 and Annex 16.2.7, Listing 16.2.7.7 for details.

10.6.4 Deaths

There were no deaths reported in the study, see EOT Table 14.3.2.3.

10.6.5 Other serious adverse events/reactions

Please refer to Section 10.6.3.1 for details on SAEs reported in the study.

10.6.6 Other significant adverse events/reactions

Please refer to Sections 10.6.3.2 and 10.6.3.3 for other significant events reported during the study.

10.6.7 Other observations related to safety

Vital signs and physical findings

There were no significant abnormal vital sign findings in the study. Vital signs are summarized in EOT Tables 14.3.6.1 to 14.3.6.3 and 14.1.6. Vital signs were measured at the first visit (visit 1) and at end of study. Individual patient profiles are presented in EOT Listing 14.3.7.1. The vital signs outside the reference range are presented in EOT Table 14.3.4.3.

Body measurements

The body measurements in the study included height and body weight. There was no significant abnormal finding related to body measurements in the study. Body measurements are summarized in EOT Tables 14.3.6.4 and 14.3.6.5. Individual patient profiles are presented in EOT Listing 14.3.7.2.

10.6.8 Pregnancy

No pregnant or lactating women were enrolled in this study (refer to Table 10-1).

10.6.9 Summary of adverse events

Primary endpoint: specific ADRs

- A total of 3 specific ADRs in 2 patients were reported in this study; 2 incidences of positive non-neutralising anti-rFXIII antibody in one patient at 2 time-points ([redacted]) and a suspected lack of therapeutic effect in another patient.
- There were no allergic reactions or embolic and thrombotic events assessed as related to rFXIII or neutralising antibodies against rFXIII reported during the study.

Secondary safety endpoints

- Of the 30 patients, a total of 18 patients reported 44 adverse events of which 11 events in 7 patients were evaluated to be possibly or probably related to the rFXIII. All the related AEs recovered.
- In total, there were 10 SAEs reported by 7 patients during the study; all the SAEs were unlikely related to the rFXIII as assessed by the investigator and all the SAEs recovered.
- There were 4 medical events of special interest reported during the study and all the events recovered.

10.7 PRO-RBDD results

As of the cut-off date of 11 November 2018, there were 4 patients (3 [redacted] and one [redacted] of [redacted] who were registered in the PRO-RBDD registry and who were on prophylaxis with rFXIII, all with endogenous FXIII:C levels < 2%. The age of the patients ranged from 20 to 41 years.

All the patients had a history of severe bleeding, such as haemarthrosis, haematoma, and umbilical cord bleeding, in addition to mucocutaneous bleeding, before prophylaxis. Out of the 4 patients, 1 patient had a post-traumatic cutaneous bleeding and 1 patient experienced epistaxis during prophylaxis with rFXIII, with no need for further treatment.

No adverse events or treatment-requiring bleeding episodes were reported as of the cut-off date of 11 November 2018. One patient reported 2 events of [redacted] and had [redacted], all of which occurred before the patient entered into the registry. There were no spontaneous bleeding episodes, no pregnancies and no major surgeries reported during the registry period. Refer to Annex 16.2.9, Listing 16.2.9.1 for more details.

11 Discussion

The multi-centre, multinational, non-interventional PASS mentor™6 study was undertaken to investigate the incidence of specific ADRs associated with the use of rFXIII in patients with congenital FXIII A-subunit deficiency, comprising anti-FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of therapeutic effect. The results show that rFXIII is safe and effective for treatment and preventing bleeds in patients with congenital FXIII-A subunit deficiency.

11.1 Key results

Safety of rFXIII

There were no safety concerns observed in this study. There were no allergic reactions, no embolic and thrombotic events assessed as related to rFXIII and no neutralising antibodies against rFXIII. There was one suspected lack of therapeutic effect reported. These findings are consistent with the safety results from previous trials in the mentor™ programme[4] [5-9] (mentor™1,[4] mentor™2[3] and mentor™5)[10] in patients with congenital FXIII A-subunit deficiency where no safety concerns were identified.

The present observational study closely evaluated and monitored for antibody development to FXIII by testing patients for anti-rFXIII antibodies. There was one case of positive low-titre transient non-neutralising anti-rFXIII antibody reported in a [redacted] The antibodies did not inhibit FXIII activity and the patient continued to be treated with rFXIII. The presence of these non-neutralising anti-rFXIII antibodies was not associated with any treatment-requiring bleeds or allergic reactions. Furthermore, the antibodies declined below the detection limit despite repeated exposure to rFXIII. Thus, the observed low-titre, non-neutralising anti-rFXIII antibodies was not clinically significant. No cases of neutralising antibodies have been seen in this study.

Allergic reactions are a potential risk associated with the administration of any protein product. No related events concerning allergic reactions have been reported in patients with congenital FXIII deficiency in this study.

The rFXIII acts at the end of the haemostatic cascade and does not initiate thrombosis. No embolic or thrombotic events assessed as related to rFXIII have been reported in this study.

Effectiveness of rFXIII

No events of lack of effect have been observed in this PASS. However, there was one case of suspected lack of therapeutic effect as assessed by the investigator in a [redacted] who repeatedly had [redacted] when [redacted]. The patient had normal FXIII in-vitro activity levels and had no anti-rFXIII antibodies.

During the study, only 6 bleeds requiring treatment with a FXIII containing product were observed in the 30 participating patients. In all cases, these bleeds were associated with trauma. Of these, a total of 5 traumatic bleeding episodes in 4 patients were treated with rFXIII, and all showed a good to excellent haemostatic response. This suggests that rFXIII can be used not only for prophylaxis, but also to treat the bleedings.

The low bleeding rate in this study can be attributed to 83% (25/30) of the patients having no bleeding episodes requiring treatment with a FXIII containing product during the entire study duration. Also, 53% (16/30) of the patients had no bleeding episodes at all. Remarkably, no spontaneous treatment-requiring bleeds occurred during the 6-year study. The patients also did not experience any intracranial bleedings during the study period.

A total of 9 minor surgeries were performed in 6 patients. Out of these, one patient had 2 minor surgeries for which [redacted] received [redacted] prior to both the surgeries.[3] The haemostatic response during and after the surgeries was good to excellent (the haemostatic response was missing for one surgery).

The overall estimated ABR for treatment-requiring bleeding episode was 0.066 bleeds/patient/year. This finding is consistent with efficacy results from the rFXIII trials (mentor™1, mentor™2 and mentor™5) in patients with congenital FXIII subunit-A deficiency.

PRO-RBDD results

No adverse events or treatment-requiring bleeding episodes were reported by the 4 patients with congenital FXIII subunit-A deficiency enrolled in the registry who were treated with rFXIII. There were no spontaneous bleeding episodes, no pregnancies and no major surgeries reported during the registry period (02 February 2012 to 11 November 2018). The results from the registry are consistent with the safety and efficacy profile otherwise observed for rFXIII.

11.2 Limitations

For potential bias, please refer Section 9.6.

From a clinical perspective the population of patients with FXIII deficiency is very limited and a study of this type with 30 patients is relatively large and within what is feasible to conduct.

11.3 Interpretation

The safety and effectiveness of rFXIII in treating patients with congenital FXIII A-subunit deficiency has been consistently demonstrated in this PASS. No allergic reactions and no embolic and thrombotic events related to rFXIII, or any other safety concerns were observed with the use of rFXIII. Remarkably, no spontaneous treatment-requiring bleeds occurred during the 6-year rFXIII prophylactic treatment period.

Based on the overall available data and the results from this PASS, the benefits of treatment with rFXIII in patients with congenital FXIII A-subunit deficiency are considered to significantly outweigh the risks.

11.4 Generalisability

The study population were the patients who based on the indication would benefit from rFXIII treatment. The results of this study could be applied only to patients with congenital FXIII A-subunit deficiency. The very few inclusion and exclusion criteria would reduce selection bias. As a multi-centre, multinational population has been selected, the generalisability of the study was evaluated as high, although the relatively low number of patients needs to be taken into consideration.

12 Other information

This section is not applicable for this report.

13 Conclusion

Data from this non-interventional PASS mentor™6 that was ongoing for 6 years between May 2013 and June 2019 showed that rFXIII (NovoThirteen®) prophylaxis every 4 weeks is effective and well tolerated. The adverse events reported did not give rise to any safety concerns and none of the patients withdrew from the study due to lack of efficacy. The observed effectiveness of rFXIII was in alignment with efficacy results from previous rFXIII clinical trials. No spontaneous treatment-requiring bleeds occurred during the 6-year study period. In addition to prophylactic treatment, rFXIII was used for treatment of traumatic bleeds and in minor surgeries with good to excellent haemostatic response. The real-world use of rFXIII and the clinical practice patterns seen in this study were in accordance with the current efficacy and safety profile of rFXIII. There were no pregnant/lactating women or patients with renal insufficiency included in the study.

In conclusion, based on the clinically identified and proven benefits of rFXIII therapy seen in this real-world observational study, and on the key risks associated with rFXIII therapy, Novo Nordisk A/S evaluates that the benefit-risk profile of rFXIII remains favourable and unchanged by 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 - full analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Age at baseline (years)				
N	13	15	[redacted]	30
Mean (SD)	9.2 (4.9)	33.9 (11.9)		25.5 (18.8)
Median				
Min ; Max				
Gender, N (%)				
N	13 (100.0)	15 (100.0)	2 (100.0)	30 (100.0)
Male	[redacted]			17 (56.7)
Female				13 (43.3)
Country, N (%)				
N	13 (100.0)	15 (100.0)	2 (100.0)	30 (100.0)
Canada	[redacted]			3 (10.0)
Denmark				4 (13.3)
Hungary				1 (3.3)
Italy				5 (16.7)
Spain				3 (10.0)
United Kingdom				1 (3.3)
United States of America				13 (43.3)
Ethnicity, N (%)				
N	13 (100.0)	15 (100.0)	2 (100.0)	30 (100.0)
Hispanic or Latino	[redacted]			6 (20.0)
Not Hispanic or Latino				22 (73.3)
NA				2 (6.7)
Race, N (%)				
N	13 (100.0)	15 (100.0)	2 (100.0)	30 (100.0)
Black Or African American	[redacted]			4 (13.3)
White				22 (73.3)
Other				3 (10.0)
NA				1 (3.3)

N: Number of patients, %: Percentage of patients, SD: Standard deviation, NA: not applicable
f13-3868/freeze_20191022_er - 22OCT2019 - t_1410_demo/14100010_demo.txt

14.1.2 Body measurements at baseline - full analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Height (cm)				
N	13	12	[redacted]2	27
Mean (SD)	134.3 (26.0)	171.5 (12.4)	[redacted](2.8)	153.9 (27.4)
Median	145.6	169.1	[redacted]	161.0
Min ; Max	95.5 ; 168.0	150.0 ; 190.5	[redacted]	95.5 ; 190.5
Body weight (kg)				
N	13	14	2	29
Mean (SD)	35.0 (19.1)	84.5 (20.7)	[redacted](0.8)	63.0 (32.0)
Median	34.1	83.0	[redacted]	64.2
Min ; Max	12.0 ; 64.2	52.5 ; 127.0	[redacted]	12.0 ; 127.0
BMI (kg/m^2)				
N	13	12	[redacted]2	27
Mean (SD)	17.7 (4.8)	29.3 (6.3)	[redacted](1.2)	23.8 (8.0)
Median	15.5	29.4	[redacted]	22.7
Min ; Max	13.2 ; 27.7	20.8 ; 39.4	[redacted]	13.2 ; 39.4

N: Number of patients, SD: Standard deviation, BMI: body mass index at baseline.
The baseline value for height and weight is the measurement at screening visit 1.
f13-3868/freeze_20191022_er - 22OCT2019 - t_1410_body/14100020_body.txt

14.1.3 Concomitant medication at baseline - full analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Any medication	13 (100.0)	14 (93.3)	2 (100.0)	29 (96.7)
Acetylsalicylic acid;magnesium oxide	-	-	1 (50.0)	1 (3.3)
Allopurinol	-	-	1 (50.0)	1 (3.3)
Aminocaproic acid	3 (23.1)	-	-	3 (10.0)
Amlodipine	-	-	1 (50.0)	1 (3.3)
Amoxicillin;clavulanate potassium	1 (7.7)	-	-	1 (3.3)
Calcium	1 (7.7)	-	-	1 (3.3)
Catridecacog	12 (92.3)	12 (80.0)	1 (50.0)	25 (83.3)
Celecoxib	-	1 (6.7)	-	1 (3.3)
Chondroitin sulfate;glucosamine sulfate	-	1 (6.7)	-	1 (3.3)
Cyclobenzaprine	-	1 (6.7)	-	1 (3.3)
Cyclobenzaprine hydrochloride	-	2 (13.3)	-	2 (6.7)
Diphenhydramine hydrochloride	-	1 (6.7)	-	1 (3.3)
Escitalopram oxalate	1 (7.7)	1 (6.7)	-	2 (6.7)
Ezetimibe	-	-	1 (50.0)	1 (3.3)
Factor XIII (fibrin stabilising factor)	11 (84.6)	7 (46.7)	1 (50.0)	19 (63.3)
Hydrocodone;paracetamol	-	1 (6.7)	-	1 (3.3)
Insulin aspart;insulin aspart protamine (crystalline)	-	-	1 (50.0)	1 (3.3)
Levetiracetam	1 (7.7)	-	-	1 (3.3)
Levothyroxine sodium	-	-	1 (50.0)	1 (3.3)
Lidocaine;prilocaine	1 (7.7)	-	-	1 (3.3)
Lorazepam	-	1 (6.7)	-	1 (3.3)
Losartan	-	-	1 (50.0)	1 (3.3)
Macrogol 3350;potassium chloride;sodium bicarbonate;sodium chloride	-	1 (6.7)	-	1 (3.3)
Magnesium	-	1 (6.7)	-	1 (3.3)
Metformin	-	-	1 (50.0)	1 (3.3)
Metformin hydrochloride;sitagliptin phosphate monohydrate	-	1 (6.7)	-	1 (3.3)
Methylphenidate hydrochloride	1 (7.7)	-	-	1 (3.3)
Minerals nos;vitamins nos	-	1 (6.7)	-	1 (3.3)
Mirabegron	-	1 (6.7)	-	1 (3.3)
Montelukast sodium	-	1 (6.7)	-	1 (3.3)
Multivitamins, plain	-	1 (6.7)	-	1 (3.3)
Not coded:Human factor*	1 (7.7)	-	-	1 (3.3)
Oxycodone hydrochloride	-	1 (6.7)	-	1 (3.3)
Pantoprazole sodium sesquihydrate	-	1 (6.7)	-	1 (3.3)
Paracetamol	1 (7.7)	3 (20.0)	-	4 (13.3)
Perindopril arginine	-	1 (6.7)	-	1 (3.3)
Phenoxymethylpenicillin	-	1 (6.7)	-	1 (3.3)
Ramipril	-	1 (6.7)	-	1 (3.3)

N: Number of patients, %: Percentage of patients
* There is no exact trade-name match in the dictionary for human factor.

f13-3868/freeze_20191022_er - 22OCT2019 - t_1410_cmed/14100040_conmed.txt

Concomitant medication at baseline - full analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Sennoside a+b	-	1 (6.7)	-	1 (3.3)
Simvastatin	-	1 (6.7)	2 (100.0)	3 (10.0)
Solifenacin succinate	-	1 (6.7)	-	1 (3.3)
Tramadol hydrochloride	-	1 (6.7)	-	1 (3.3)
Tranexamic acid	-	1 (6.7)	-	1 (3.3)
Valaciclovir hydrochloride	-	1 (6.7)	-	1 (3.3)
Vitamin d nos	1 (7.7)	-	-	1 (3.3)
Vitamins nos	2 (15.4)	-	-	2 (6.7)

N: Number of patients, %: Percentage of patients
* There is no exact trade-name match in the dictionary for human factor.

14.1.4 Concomitant illness at baseline - full analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Any illness	6 (46.2)	9 (60.0)	2 (100.0)	17 (56.7)
ADHD	-	1 (6.7)	-	1 (3.3)
Abortion of ectopic pregnancy	[redacted]			
Allergy to insect sting	-	1 (6.7)	-	1 (3.3)
Ankle fracture	-	1 (6.7)	-	1 (3.3)
Arthritis	-	1 (6.7)	-	1 (3.3)
Bronchitis	-	1 (6.7)	-	1 (3.3)
Cataract (right)	-	-	1 (50.0)	1 (3.3)
Cerebellar hemorrhage	-	1 (6.7)	-	1 (3.3)
Cerebral haemorrhage	-	-	1 (50.0)	1 (3.3)
Cerebral hemorrhage	-	1 (6.7)	-	1 (3.3)
Cerebral hemorrhage traumatic	-	1 (6.7)	-	1 (3.3)
Cognitive disorder	-	1 (6.7)	-	1 (3.3)
Degenerative disc disease	-	1 (6.7)	-	1 (3.3)
Depression	-	1 (6.7)	-	1 (3.3)
Dislocated shoulder	-	1 (6.7)	-	1 (3.3)
Epistaxis	1 (7.7)	-	-	1 (3.3)
Eye operation	-	1 (6.7)	-	1 (3.3)
Factor XIII deficiency	[redacted]			
Fatigue	-	1 (6.7)	-	1 (3.3)
Femur fracture	-	1 (6.7)	-	1 (3.3)
Fibromyalgia	-	1 (6.7)	-	1 (3.3)
Gallstones	-	1 (6.7)	-	1 (3.3)
Gastritis	-	1 (6.7)	-	1 (3.3)
Gastroesophageal reflux disease	-	1 (6.7)	-	1 (3.3)
Headache	-	2 (13.3)	-	2 (6.7)
Hepatitis C virus test positive	-	1 (6.7)	-	1 (3.3)
Herpes simplex type II	[redacted]			
Hip fracture	-	1 (6.7)	-	1 (3.3)
Hirsutism	-	1 (6.7)	-	1 (3.3)
Hypercholesterolaemia	-	-	1 (50.0)	1 (3.3)
Hypercholesterolemia	-	-	1 (50.0)	1 (3.3)
Hypertension	-	-	1 (50.0)	1 (3.3)
Hyperuricemia	-	-	1 (50.0)	1 (3.3)
Hyphema	1 (7.7)	-	-	1 (3.3)
Hypothyroidism	-	-	1 (50.0)	1 (3.3)
Intracranial haemorrhage	1 (7.7)	-	-	1 (3.3)
Intracranial hemorrhage	-	1 (6.7)	-	1 (3.3)
Joint pain	-	1 (6.7)	-	1 (3.3)
Low back pain	-	1 (6.7)	-	1 (3.3)
Major depressive disorder	1 (7.7)	-	-	1 (3.3)
Menometrorrhagia	-	1 (6.7)	-	1 (3.3)
Monoclonal gammopathy of unknown significance	[redacted]			
Motor vehicle accident	[redacted]			
Mucocele of mouth	-	1 (6.7)	-	1 (3.3)
Muscle bleeding	-	1 (6.7)	-	1 (3.3)
Muscle degeneration	-	1 (6.7)	-	1 (3.3)
Muscle hemorrhage	-	1 (6.7)	-	1 (3.3)
Nephrectomy	-	1 (6.7)	-	1 (3.3)
Obesity	-	1 (6.7)	-	1 (3.3)
Ovarian bleeding	[redacted]			
Ovary removal				

N: Number of patients, %: Percentage of patients
f13-3868/freeze_20191022_er - 22OCT2019 - t_1410_cill/14100050_conill.txt

Concomitant illness at baseline - full analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Paraplegia	-	1 (6.7)	-	1 (3.3)
Penicillin allergy	-	1 (6.7)	-	1 (3.3)
Persistent cough	-	1 (6.7)	-	1 (3.3)
Phlebitis superficial	-	-	1 (50.0)	1 (3.3)
Pinkeye	-	1 (6.7)	-	1 (3.3)
Pneumonia	-	1 (6.7)	-	1 (3.3)
Post procedural bleeding	-	1 (6.7)	-	1 (3.3)
Rupture spleen	-	1 (6.7)	1 (50.0)	2 (6.7)
Seasonal allergy	-	2 (13.3)	-	2 (6.7)
Seizures	[redacted]			
Sexual desire disorder				
Sinus infection	-	1 (6.7)	-	1 (3.3)
Smoker	-	1 (6.7)	-	1 (3.3)
Snoring	1 (7.7)	-	-	1 (3.3)
Spinal fusion	-	-	1 (50.0)	1 (3.3)
Spinal laminectomy	-	1 (6.7)	-	1 (3.3)
Splenectomy	-	-	1 (50.0)	1 (3.3)
Tibia pain	-	1 (6.7)	-	1 (3.3)
Tooth extraction	-	1 (6.7)	-	1 (3.3)
Type II diabetes mellitus	-	-	1 (50.0)	1 (3.3)
Urethral dilation procedure	-	-	1 (50.0)	1 (3.3)
Urethral stricture	-	-	1 (50.0)	1 (3.3)
VIth nerve disorder	-	-	1 (50.0)	1 (3.3)
Vertebral fracture	-	1 (6.7)	-	1 (3.3)
Viral upper respiratory tract infection	-	1 (6.7)	-	1 (3.3)
Vitamin D deficiency	1 (7.7)	-	-	1 (3.3)

N: Number of patients, %: Percentage of patients
f13-3868/freeze_20191022_er - 22OCT2019 - t_1410_cill/14100050_conill.txt

14.1.5 Pre-defined complications - full analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Allergic reaction to pharmaceutical drug	-	6 (40.0)	-	6 (20.0)
History of embolic and/Or thrombotic events	-	-	2 (100.0)	2 (6.7)

N: Number of patients, %: Percentage of patients
f13-3868/freeze_20191022_er - 22OCT2019 - t_1410_complications/14100060_complications.txt

14.1.6 Vital signs at baseline - full analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Diastolic blood pressure (mmHg)				
N	10	13	2	25
Mean (SD)	60.2 (6.8)	76.8 (11.2)	[redacted] (2.8)	70.3 (12.3)
Median	60.0	74.0	[redacted]	72.0
Min ; Max	53.0 ; 75.0	60.0 ; 105.0	[redacted]	53.0 ; 105.0
Systolic blood pressure (mmHg)				
N	10	13	2	25
Mean (SD)	104.2 (10.0)	123.3 (15.9)	[redacted] (15.6)	117.1 (17.7)
Median	103.5	120.0	[redacted]	117.0
Min ; Max	91.0 ; 120.0	100.0 ; 157.0	[redacted]	91.0 ; 157.0
Pulse (beats/min)				
N	11	13	2	26
Mean (SD)	84.5 (10.9)	78.2 (11.4)	[redacted] (4.9)	80.0 (11.6)
Median	84.0	75.0	[redacted]	76.5
Min ; Max	66.0 ; 101.0	63.0 ; 105.0	[redacted]	63.0 ; 105.0

N: Number of patients, SD: Standard deviation
f13-3868/freeze_20191022_er - 22OCT2019 - t_1410_vitals/14100065_vitals.txt

14.1.7 Haemophilia history - full analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Underlying gene defect, N (%)				
Yes				
No				
Unknown				
Diagnosis of haemophilia, N (%)				
FXIII Deficiency				
NA				
Specify FXIII deficiency, N (%)				
Heterozygous				
Homozygous				
Unknown				
NA				
NK				
FXIII level (IU/mL) at diagnosis*, N (%)				
0.05				
FXIII level (%) at diagnosis*, N (%)				
.05				
0				
1				
16				
18				
22				
3				
4				
5				
<03				
<10%				
<15				
Current FXIII (IU/mL) level*, N (%)				
0.258				
0.31				
0.325				
0.7				

N: Number of patients, %: Percentage of patients
*Patients could either report the value as numeric or in ranges.

Haemophilia history - full analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Current FXIII (%) level*, N (%)				
0				
03.8				
14				
14.7				
15				
15.1				
16				
17				
21				
24				
5				
6				
<04				
<15				
<4				
History of FXIII antibodies, N (%)				
No				
Yes				
Antibodies nature detected in the past, N (%)				
NA				
Past FXIII antibodies, N (%)				
No				
Most recent antibody value (BU/mL), N (%)				
0				
1				
NA				
ND				

N: Number of patients, %: Percentage of patients
*Patients could either report the value as numeric or in ranges.

14.1.8 Genotype - full analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Gene type, N (%)				
N				
F13 SUBUNIT A				
FXIII				
OTHER				
Genotype performed, N (%)				
N				
No				
Yes				
Mutation identified, N (%)				
N				
No				
Yes				
Mutation type, N (%)				
N				
Splice site mutation				
Deletions				
Substitution				
Substitution, N (%)				
N				
Missense Mutations				
Nonsense Mutations				
Missense:R77C ,Nonsense: R171X				
Splice Site Mutation				
NA*				
Sequence variant, N (%)				
N				
DNA level				
Protein level				

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.
* These patients have no genotype information available.

f13-3868/freeze_20191022_er - 22OCT2019 - t_1410_geno/14100080_geno.txt

14.1.9 Family haemophilia history - full analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Family history in 1st degree relatives:				
Antibodies history towards FXIII, N (%)				
N	5 (100.0)	3 (100.0)	2 (100.0)	10 (100.0)
No	3 (60.0)	1 (33.3)	2 (100.0)	6 (60.0)
Unknown	2 (40.0)	2 (66.7)	-	4 (40.0)
Congenital haemostatic disorder, N (%)				
N	7 (100.0)	7 (100.0)	-	14 (100.0)
FXIII congenital deficiency	7 (100.0)	6 (85.7)	-	13 (92.9)
Other	-	1 (14.3)	-	1 (7.1)
FXIII deficiency type, N (%)				
N	7 (100.0)	6 (100.0)	-	13 (100.0)
Heterozygous	2 (28.6)	4 (66.7)	-	6 (46.2)
Homozygous	5 (71.4)	1 (16.7)	-	6 (46.2)
Nk	-	1 (16.7)	-	1 (7.7)
Congenital pro-thrombotic disorders (Y/N), N (%)				
N	10 (100.0)	15 (100.0)	3 (100.0)	28 (100.0)
No	10 (100.0)	15 (100.0)	3 (100.0)	28 (100.0)
Family history in other relatives:				
Antibodies history towards FXIII, N (%)				
N	5 (100.0)	3 (100.0)	2 (100.0)	10 (100.0)
No	5 (100.0)	1 (33.3)	2 (100.0)	8 (80.0)
Unknown	-	2 (66.7)	-	2 (20.0)
Congenital haemostatic disorder, N (%)				
N	4 (100.0)	2 (100.0)	-	6 (100.0)
FXIII congenital deficiency	4 (100.0)	2 (100.0)	-	6 (100.0)
FXIII deficiency type, N (%)				
N	4 (100.0)	1 (100.0)	-	5 (100.0)
Heterozygous	2 (50.0)	1 (100.0)	-	3 (60.0)
Homozygous	2 (50.0)	-	-	2 (40.0)
Congenital pro-thrombotic disorders (Y/N), N (%)				
N	9 (100.0)	12 (100.0)	3 (100.0)	24 (100.0)
No	9 (100.0)	12 (100.0)	3 (100.0)	24 (100.0)

N: Number of patients, %: Percentage of patients
f13-3868/freeze_20191022_er - 22OCT2019 - t_1410_genhist/14100090_genhist.txt

14.1.10 Participation in registries - full analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Participation in other registry, N (%)				
PRO-RBDD				
Other				
ATHN DATASET				
CANADIAN HEMOPHILIA SOCIETY OF RARE BLEEDING DISORDERS.				
CBDR				
CDC				
CDC SURVEILLANCE				
COMMUNITY COUNTS RARE COAGULATION DISORDERS				
EUHASS				
EUHASS, NHD				

N: Number of patients, %: Percentage of patients
f13-3868/freeze_20191022_er - 22OCT2019 - t_1410_registry/14100100_registry.txt

14.1.11 Treatment history - full analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Current treatment prior to study, N (%)				
Prophylaxis	12 (92.3)	11 (73.3)	2 (100.0)	25 (83.3)
On-demand	-	1 (6.7)	-	1 (3.3)
Supplemental on-demand	1 (7.7)	3 (20.0)	-	4 (13.3)
Previous prophylaxis patients:				
Product given, N (%)				
Cluviat	-	1 (6.7)	-	1 (3.3)
FXIIIr (novothirteen)	-	1 (6.7)	-	1 (3.3)
Factor 13 a-subunit recombinanat (tetten)	1 (7.7)	-	-	1 (3.3)
Factor 13a - Submit, Recombinant(Tretten)	-	1 (6.7)	-	1 (3.3)
Fibro-gamin	-	-	1 (50.0)	1 (3.3)
Fibrogamin	1 (7.7)	2 (13.3)	-	3 (10.0)
Novo 13	-	-	1 (50.0)	1 (3.3)
Novo-thirteen catridecacog	-	1 (6.7)	-	1 (3.3)
Novotherteen	-	1 (6.7)	-	1 (3.3)
Novothirteen	1 (7.7)	2 (13.3)	-	3 (10.0)
Novothirtheen	2 (15.4)	-	-	2 (6.7)
Tranexamic Acid	-	1 (6.7)	-	1 (3.3)
Tretten	9 (69.2)	6 (40.0)	-	15 (50.0)
Tretten / rFXIII	-	1 (6.7)	-	1 (3.3)
Frequency of dosing, N (%)				
Once	-	1 (6.7)	-	1 (3.3)
Once Every 28 Days	-	-	1 (50.0)	1 (3.3)
Monthly	7 (53.8)	8 (53.3)	-	15 (50.0)
28 Days	-	1 (6.7)	-	1 (3.3)
37-42 Days	1 (7.7)	-	-	1 (3.3)
Every 35 Days	-	1 (6.7)	-	1 (3.3)
Every 28 Days	2 (15.4)	1 (6.7)	-	3 (10.0)
Every Third Week	-	-	1 (50.0)	1 (3.3)
Every 4-5 Weeks	-	1 (6.7)	-	1 (3.3)
Every4 Weeks	1 (7.7)	-	-	1 (3.3)
Every 5 Weeks	2 (15.4)	-	-	2 (6.7)
Bleeding episodes within the 24 months				
Treatment requiring				
N	9	13	2	24
Mean (SD)	0.11 (0.33)	0.15 (0.38)	0.50 (0.71)	0.17 (0.38)
Median	0.00	0.00	0.50	0.00
Min ; Max	0 ; 1	0 ; 1	0 ; 1	0 ; 1
Non-treatment requiring				
N	8	12	1	21
Mean (SD)	2.13 (4.52)	0.33 (0.78)	0.00 (-)	1.00 (2.88)
Median	0.00	0.00	0.00	0.00
Min ; Max	0 ; 13	0 ; 2	0 ; 0	0 ; 13

N: Number of patients, %: Percentage of patients
* Patients can consume more than one product.

Treatment history - full analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Previous on-demand patients:				
Product given*, N (%)				
Fibrogammin	-	2 (13.3)	-	2 (6.7)
Heparinoid gel	-	1 (6.7)	-	1 (3.3)
Bleeding episodes within the 24 months				
Treatment requiring				
N	0	0	0	0
Mean (SD)	- (-)	- (-)	- (-)	- (-)
Median	-	-	-	-
Min ; Max	- ; -	- ; -	- ; -	- ; -
Non-treatment requiring				
N	0	0	0	0
Mean (SD)	- (-)	- (-)	- (-)	- (-)
Median	-	-	-	-
Min ; Max	- ; -	- ; -	- ; -	- ; -
Surgeries (all patients):				
Type of surgery, N (%)				
Elective Surgery Minor Surgery	-	-	1 (50.0)	1 (3.3)
Minor Surgery Elective Surgery	-	-	1 (50.0)	1 (3.3)
FXIII prod during surgery, N (%)				
Fibrogamin	-	-	1 (50.0)	1 (3.3)

N: Number of patients, %: Percentage of patients
* Patients can consume more than one product.

14.2 Efficacy data

14.2.1 Patient disposition - summary - full analysis set

	Children < 18 years	Adults (18 - 65 years)	Elderly > 65 years	Total
Screened	13	15	2	30
Exposed	13(100.0)	15(100.0)	2(100.0)	30(100.0)
Withdrawal	1(7.7)	3(20.0)	1(50.0)	5(16.7)
Withdrawal Criteria:W1	1(7.7)	1(6.7)	0(0.0)	2(6.7)
Withdrawal Criteria:W3	0(0.0)	0(0.0)	1(50.0)	1(3.3)
Other	0(0.0)	2(13.3)	0(0.0)	2(6.7)
Completed study	12(92.3)	12(80.0)	1(50.0)	25(83.3)
Full analysis set	13(100.0)	15(100.0)	2(100.0)	30(100.0)
Safety analysis set	13(100.0)	15(100.0)	2(100.0)	30(100.0)
Years in study	37.0	34.4	3.9	75.3
EDs in study	431	404	53	888
Undergone minor surgery*	3(23.1)	3(20.0)	0(0.0)	6(20.0)
Undergone major surgery**	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Patients with renal insufficiency	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Pregnant or lactating women	0(0.0)	0(0.0)	0(0.0)	0(0.0)

N: Number of patients, %: Percentage of exposed patients, * Minor surgery during study
** Major surgery during study
The full analysis set and the safety analysis set both consists of all patients exposed to rFXIII.
ED: Exposure days

f13-3868/freeze_20191022_er - 22OCT2019 - t_1420_patdisp/14200010_subj_disp.txt

14.2.2 Consumption of rFXIII during the study - full analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Consumption used for treatment* per year per patient** (IU/kg/year)				
N	13	15	2	30
Mean (SD)	470.2 (195.79)	337.8 (89.41)	349.1 (3.24)	395.9 (155.23)
Median	452.5	348.4	349.1	404.1
Min ; Max	154.2 ; 982.3	173.7 ; 456.6	346.8 ; 351.4	154.2 ; 982.3
Average prophylaxis dose*** (IU/kg)				
N	420	364	53	837
Mean (SD)	43.7 (12.57)	31.3 (7.71)	26.9 (0.84)	37.2 (12.16)
Median	38.9	31.2	26.7	35.7
Min ; Max	30.3 ; 89.7	18.2 ; 50.7	26.0 ; 28.7	18.2 ; 89.7
Average dose for treatment of bleed from start to stop of bleed+ (IU/kg/bleed)				
N	4	1	0	5
Mean (SD)	42.2 (7.73)	36.0 (-)	- (-)	41.0 (7.24)
Median	39.6	36.0	-	37.6
Min ; Max	36.3 ; 53.3	36.0 ; 36.0	- ; -	36.0 ; 53.3

*Consumption used for treatment includes all doses given (prophylaxis, treatment of bleed)
The contribution from the last prophylactic dose given is adjusted to the remaining relative part of planned dosing interval of 28 days up to the cut-off date
**N is number of patients
***N is number of doses
+N is number of bleeds

f13-3868/freeze_20191022_er - 22OCT2019 - t_1420_cons/14200020_cons.txt

14.2.3 Exposure of rFXIII during the study - full analysis set

	Prophylaxis	On-demand	Total
Number of patients	30	-	30
Total number of doses per patient			
N	30	-	30
Mean (SD)	29.6 (16.8)		29.6 (16.8)
Median	28.0		28.0
Min ; Max	1 ; 70		1 ; 70
Total number of exposure days per patient			
N	30	-	30
Mean (SD)	29.6 (16.8)		29.6 (16.8)
Median	28.0		28.0
Min ; Max	1 ; 70		1 ; 70
Total number of doses used for treatment of bleed per patient			
N	4	-	4
Mean (SD)	1.3 (0.5)		1.3 (0.5)
Median	1.0		1.0
Min ; Max	1 ; 2		1 ; 2

14.2.4 Details of bleeding episodes - Full analysis set

	Treatment requiring N (%)	Non Treatment requiring N (%)	All N (%)
Number of patients	30	30	30
Number of patients with bleeds	5	10	14
Number of bleeds	6	59	65
Cause of bleed			
N	6 (100.0)	50 (100.0)	56 (100.0)
Spontaneous	-	30 (60.0)	30 (53.6)
Traumatic	6 (100.0)	18 (36.0)	24 (42.9)
Nk	-	2 (4.0)	2 (3.6)
Severity of bleed			
N	6 (100.0)	6 (100.0)	12 (100.0)
Mild/Moderate	6 (100.0)	6 (100.0)	12 (100.0)
Site of bleed			
N	6 (100.0)	59 (100.0)	65 (100.0)
Haemarthrosis	1 (16.7)	-	1 (1.5)
Muscular	-	1 (1.7)	1 (1.5)
Subcutaneous	1 (16.7)	7 (11.9)	8 (12.3)
Other	4 (66.7)	51 (86.4)	55 (84.6)
Treatment used			
N	7 (100.0)	4 (100.0)	11 (100.0)
RFXIII	5 (71.4)	-	5 (45.5)
Other haemostatic product			
AMINOCAPROIC ACID	-	4 (100.0)	4 (36.4)
CYKLONOVA	1 (14.3)	-	1 (9.1)
Fibrogammin	1 (14.3)	-	1 (9.1)
Therapy other than haemostatic drug			
N	-	6 (100.0)	6 (100.0)
COMPRESSION	-	4 (66.7)	4 (66.7)
ICE	-	1 (16.7)	1 (16.7)
OTHER	-	1 (16.7)	1 (16.7)

N: Number of bleeds, %: Percentage of bleeds
Bleeding episodes treated with FXIII containing products are defined as treatment requiring bleeding episodes
Haemostatic response is summarised only for treatment requiring bleeding episodes

Details of bleeding episodes - Full analysis set

	Treatment requiring N (%)	Non Treatment requiring N (%)	All N (%)
Haemostatic response			
N	6 (100.0)	-	6 (100.0)
Excellent	4 (66.7)	-	4 (66.7)
Good	2 (33.3)	-	2 (33.3)

N: Number of bleeds, %: Percentage of bleeds
Bleeding episodes treated with FXIII containing products are defined as treatment requiring bleeding episodes
Haemostatic response is summarised only for treatment requiring bleeding episodes

14.2.5 Details of bleeding episode during home treatment

	Treatment requiring N (%)	Non Treatment requiring N (%)	All N (%)
Number of patients	30	30	30
Number of patients with bleeds	4	9	12
Number of bleeds	5	53	58
Cause of bleed			
N	5 (100.0)	44 (100.0)	49 (100.0)
Spontaneous	-	29 (65.9)	29 (59.2)
Traumatic	5 (100.0)	14 (31.8)	19 (38.8)
Nk	-	1 (2.3)	1 (2.0)
Severity of bleed			
N	5 (100.0)	6 (100.0)	11 (100.0)
Mild/Moderate	5 (100.0)	6 (100.0)	11 (100.0)
Site of bleed			
N	5 (100.0)	53 (100.0)	58 (100.0)
Haemarthrosis	1 (20.0)	-	1 (1.7)
Muscular	-	1 (1.9)	1 (1.7)
Subcutaneous	-	3 (5.7)	3 (5.2)
Other	4 (80.0)	49 (92.5)	53 (91.4)
Treatment used			
N	6 (100.0)	4 (100.0)	10 (100.0)
RFXIII	5 (83.3)	-	5 (50.0)
Other haemostatic product			
AMINOCAPROIC ACID	-	4 (100.0)	4 (40.0)
CYKLONOVA	1 (16.7)	-	1 (10.0)
Therapy other than haemostatic drug			
N	-	6 (100.0)	6 (100.0)
COMPRESSION	-	4 (66.7)	4 (66.7)
ICE	-	1 (16.7)	1 (16.7)
OTHER	-	1 (16.7)	1 (16.7)

N: Number of bleeds, %: Percentage of bleeds
Bleeding episodes treated with FXIII containing products are defined as treatment requiring bleeding episodes
Haemostatic response is summarised only for treatment requiring bleeding episodes

Details of bleeding episode during home treatment

	Treatment requiring N (%)	Non Treatment requiring N (%)	All N (%)
Haemostatic response			
N	5 (100.0)	-	5 (100.0)
Excellent	4 (80.0)	-	4 (80.0)
Good	1 (20.0)	-	1 (20.0)

N: Number of bleeds, %: Percentage of bleeds
Bleeding episodes treated with FXIII containing products are defined as treatment requiring bleeding episodes
Haemostatic response is summarised only for treatment requiring bleeding episodes

14.2.6 Duration of Bleeds - Full analysis set

	Treatment requiring	Non Treatment requiring	All
Number of patients	30	30	30
Number of patients with bleeds	5	10	14
Number of bleeds	6	59	65
Number of bleeds with missing stop time	-	10	10
Duration of bleed (hours)			
N	6	49	55
Mean (SD)	36.5 (35.5)	31.5 (49.5)	32.1 (48.0)
Median	34.6	23.0	23.0
Min ; Max	1 ; 96	1 ; 264	1 ; 264

Duration and time in relation to onset, dose and stop is only calculated if complete time points are available.

14.2.7 Details of surgery - Full analysis set

	Children < 18 years N (%)	Adults (18 - 65 years) N (%)	Elderly > 65 years N (%)	Total N (%)
Number of patients	13	15	2	30
Number of patients who had surgery	3	3	-	6
Number of surgeries	3	6	-	9
Type of surgery				
N	3 (100.0)	6 (100.0)	-	9 (100.0)
MINOR SURGERY	3 (100.0)	6 (100.0)	-	9 (100.0)
Haemostatic response during surgery				
N	3 (100.0)	6 (100.0)	-	9 (100.0)
EXCELLENT	1 (33.3)	4 (66.7)	-	5 (55.6)
GOOD	2 (66.7)	1 (16.7)	-	3 (33.3)
Missing		1 (16.7)	-	1 (11.1)
Haemostatic response after surgery				
N	3 (100.0)	6 (100.0)	-	9 (100.0)
EXCELLENT	1 (33.3)	3 (50.0)	-	4 (44.4)
GOOD	2 (66.7)	2 (33.3)	-	4 (44.4)
Missing		1 (16.7)	-	1 (11.1)

14.2.8 Annualised bleeding rate of all bleeding episodes - Full analysis set

	Treatment requiring	Non Treatment requiring	All
Number of patients	30	30	30
Number of patients with bleed	5	10	14
Total number of bleeds	6	59	65
Range of bleedings	0 ; 2	0 ; 41	0 ; 41
Mean bleedings per patient	0.200	1.967	2.167
Mean observation period (days)	916.5	916.5	916.5
Total observation period (years)	75.3	75.3	75.3
Poisson analysis*			
Annualised bleeding rate	0.066	0.784	0.850
95% CI	0.029 ; 0.150	0.204 ; 3.011	0.246 ; 2.940

* A 95% CI for the annualised bleeding rate is estimated from a Poisson analysis with over-dispersion if the number of bleeds is greater than 1, otherwise only the Poisson estimate is provided assuming no over-dispersion.

f13-3868/freeze_20191022_er - 22OCT2019 - t_1420_bleed_rate/14200060_bl_rate_all.txt

14.2.9 Annualised bleeding rate by cause of bleeding - full analysis set

	Treatment requiring	Non Treatment requiring	All
Number of patients	30	30	30
Spontaneous bleeding episode			
Number of patients with bleed	0	4	4
Total number of bleeds	0	30	30
Range of bleedings	0 ; 0	0 ; 27	0 ; 27
Mean bleedings per patient	0.000	1.000	1.000
Mean observation period (days)	916.5	916.5	916.5
Total observation period (years)	75.3	75.3	75.3
Poisson analysis*			
Annualised bleeding rate	0.000	0.399	0.399
95% CI	NA	0.069 ; 2.290	0.069 ; 2.290
Traumatic bleeding episode			
Number of patients with bleed	5	7	11
Total number of bleeds	6	18	24
Range of bleedings	0 ; 2	0 ; 7	0 ; 9
Mean bleedings per patient	0.200	0.600	0.800
Mean observation period (days)	916.5	916.5	916.5
Total observation period (years)	75.3	75.3	75.3
Poisson analysis*			
Annualised bleeding rate	0.066	0.239	0.306
95% CI	0.029 ; 0.150	0.112 ; 0.508	0.157 ; 0.593

CI: Confidence interval.
* A 95% CI for the annualised bleeding rate is estimated from a Poisson analysis with over-dispersion if the number of bleeds is greater than 1, otherwise only the Poisson estimate is provided assuming no over-dispersion.

f13-3868/freeze_20191022_er - 22OCT2019 - t_1420_bleed_rate/14200070_bl_cause.txt

14.2.10 Annualised bleeding rate by bleeding severity - full analysis set

	Treatment requiring	Non Treatment requiring	All
Number of patients	30	30	30
Mild/Moderate bleeding episode			
Number of patients with bleed	5	2	7
Total number of bleeds	6	6	12
Range of bleedings	0 ; 2	0 ; 5	0 ; 5
Mean bleedings per patient	0.200	0.200	0.400
Mean observation period (days)	916.5	916.5	916.5
Total observation period (years)	75.3	75.3	75.3
Poisson analysis*			
Annualised bleeding rate	0.066	0.080	0.146
95% CI	0.029 ; 0.150	0.016 ; 0.408	0.058 ; 0.369

CI: Confidence interval, NA: Not applicable.
* A 95% CI for the annualised bleeding rate is estimated from a Poisson analysis with over-dispersion if the number of bleeds is greater than 1, otherwise only the Poisson estimate is provided assuming no over-dispersion.

f13-3868/freeze_20191022_er - 22OCT2019 - t_1420_bleed_rate/14200090_bl_sev.txt

14.2.11 Annualised bleeding rate by site of bleeding - full analysis set

	Treatment requiring	Non Treatment requiring	All
Number of patients	30	30	30
Haemarthrosis bleeding episode			
Number of patients with bleed	1	0	1
Total number of bleeds	1	0	1
Range of bleedings	0 ; 1	0 ; 0	0 ; 1
Mean bleedings per patient	0.033	0.000	0.033
Mean observation period (days)	916.5	916.5	916.5
Total observation period (years)	75.3	75.3	75.3
Poisson analysis*			
Annualised bleeding rate	0.013	0.000	0.013
95% CI	NA	NA	NA
Muscular bleeding episode			
Number of patients with bleed	0	1	1
Total number of bleeds	0	1	1
Range of bleedings	0 ; 0	0 ; 1	0 ; 1
Mean bleedings per patient	0.000	0.033	0.033
Mean observation period (days)	916.5	916.5	916.5
Total observation period (years)	75.3	75.3	75.3
Poisson analysis*			
Annualised bleeding rate	0.000	0.013	0.013
95% CI	NA	NA	NA

CI: Confidence interval, NA: Not applicable.
* A 95% CI for the annualised bleeding rate is estimated from a Poisson analysis with over-dispersion if the number of bleeds is greater than 1, otherwise only the Poisson estimate is provided assuming no over-dispersion.

Annualised bleeding rate by site of bleeding - full analysis set

	Treatment requiring	Non Treatment requiring	All
Subcutaneous bleeding episode			
Number of patients with bleed	1	2	3
Total number of bleeds	1	7	8
Range of bleedings	0 ; 1	0 ; 6	0 ; 6
Mean bleedings per patient	0.033	0.233	0.267
Mean observation period (days)	916.5	916.5	916.5
Total observation period (years)	75.3	75.3	75.3
Poisson analysis*			
Annualised bleeding rate	0.013	0.093	0.093
95% CI	NA	0.028 ; 0.309	0.028 ; 0.309
Other bleeding episode			
Number of patients with bleed	4	10	13
Total number of bleeds	4	51	55
Range of bleedings	0 ; 1	0 ; 40	0 ; 40
Mean bleedings per patient	0.133	1.700	1.833
Mean observation period (days)	916.5	916.5	916.5
Total observation period (years)	75.3	75.3	75.3
Poisson analysis*			
Annualised bleeding rate	0.053	0.677	0.731
95% CI	0.023 ; 0.125	0.149 ; 3.087	0.180 ; 2.968

CI: Confidence interval, NA: Not applicable.
* A 95% CI for the annualised bleeding rate is estimated from a Poisson analysis with over-dispersion if the number of bleeds is greater than 1, otherwise only the Poisson estimate is provided assuming no over-dispersion.

14.2.12 Annualised bleeding rate of bleeding episodes by haemostatic treatment administered - Full analysis set

	Treatment requiring	Non Treatment requiring	All
Number of patients	30	30	30
RFXIII			
Number of patients with bleed	4	0	4
Total number of bleeds	5	0	5
Range of bleedings	0 ; 2	0 ; 0	0 ; 2
Mean bleedings per patient	0.167	0.000	0.167
Mean observation period (days)	916.5	916.5	916.5
Total observation period (years)	75.3	75.3	75.3
Poisson analysis*			
Annualised bleeding rate	0.066	0.000	0.066
95% CI	0.029 ; 0.150	NA	0.029 ; 0.150
AMINOCAPROIC ACID			
Number of patients with bleed	0	2	2
Total number of bleeds	0	4	4
Range of bleedings	0 ; 0	0 ; 3	0 ; 3
Mean bleedings per patient	0.000	0.133	0.133
Mean observation period (days)	916.5	916.5	916.5
Total observation period (years)	75.3	75.3	75.3
Poisson analysis*			
Annualised bleeding rate	0.000	0.053	0.053
95% CI	NA	0.012 ; 0.238	0.012 ; 0.238

CI: Confidence interval, NA: Not applicable.
* A 95% CI for the annualised bleeding rate is estimated from a Poisson analysis with over-dispersion if the number of bleeds is greater than 1, otherwise only the Poisson estimate is provided assuming no over-dispersion.

Annualised bleeding rate of bleeding episodes by haemostatic treatment administered - Full analysis set

	Treatment requiring	Non Treatment requiring	All
Fibrogammin			
Number of patients with bleed	1	0	1
Total number of bleeds	1	0	1
Range of bleedings	0 ; 1	0 ; 0	0 ; 1
Mean bleedings per patient	0.033	0.000	0.033
Mean observation period (days)	916.5	916.5	916.5
Total observation period (years)	75.3	75.3	75.3
Poisson analysis*			
Annualised bleeding rate	0.013	0.000	0.013
95% CI	NA	NA	NA

CI: Confidence interval, NA: Not applicable.
* A 95% CI for the annualised bleeding rate is estimated from a Poisson analysis with over-dispersion if the number of bleeds is greater than 1, otherwise only the Poisson estimate is provided assuming no over-dispersion.

14.2.13 Annualised bleeding rate by haemostatioc response - full analysis set

	Treatment requiring	Non Treatment requiring	All
Number of patients	30	30	30
Excellent			
Number of patients with bleed	3	2	5
Total number of bleeds	4	2	6
Range of bleedings	0 ; 2	0 ; 1	0 ; 2
Mean bleedings per patient	0.133	0.067	0.200
Mean observation period (days)	916.5	916.5	916.5
Total observation period (years)	75.3	75.3	75.3
Poisson analysis*			
Annualised bleeding rate	0.053	0.027	0.080
95% CI	0.020 ; 0.140	0.008 ; 0.091	0.039 ; 0.164
Good			
Number of patients with bleed	2	1	3
Total number of bleeds	2	2	4
Range of bleedings	0 ; 1	0 ; 2	0 ; 2
Mean bleedings per patient	0.067	0.067	0.133
Mean observation period (days)	916.5	916.5	916.5
Total observation period (years)	75.3	75.3	75.3
Poisson analysis*			
Annualised bleeding rate	0.013	0.027	0.040
95% CI	0.003 ; 0.067	0.004 ; 0.186	0.010 ; 0.159

CI: Confidence interval, NA: Not applicable.
* A 95% CI for the annualised bleeding rate is estimated from a Poisson analysis with over-dispersion if the number of bleeds is greater than 1, otherwise only the Poisson estimate is provided assuming no over-dispersion.

Annualised bleeding rate by haemostatioc response - full analysis set

	Treatment requiring	Non Treatment requiring	All
None			
Number of patients with bleed	0	1	1
Total number of bleeds	0	1	1
Range of bleedings	0 ; 0	0 ; 1	0 ; 1
Mean bleedings per patient	0.000	0.033	0.033
Mean observation period (days)	916.5	916.5	916.5
Total observation period (years)	75.3	75.3	75.3
Poisson analysis*			
Annualised bleeding rate	0.000	0.013	0.013
95% CI	NA	NA	NA

CI: Confidence interval, NA: Not applicable.
* A 95% CI for the annualised bleeding rate is estimated from a Poisson analysis with over-dispersion if the number of bleeds is greater than 1, otherwise only the Poisson estimate is provided assuming no over-dispersion.

14.2.14 Annualised bleeding rate by age - full analysis set

	Treatment requiring	Non Treatment requiring	All
Number of patients	30	30	30
Children<18 years			
Number of patients with bleed	3	7	9
Total number of bleeds	4	55	59
Range of bleedings	0 ; 2	0 ; 41	0 ; 41
Mean bleedings per patient	0.308	4.231	4.538
Mean observation period (days)	1038.7	1038.7	1038.7
Total observation period (years)	37.0	37.0	37.0
Poisson analysis*			
Annualised bleeding rate	0.108	1.488	1.596
95% CI	0.043 ; 0.275	0.343 ; 6.460	0.408 ; 6.238
Adult 18 to 65 years			
Number of patients with bleed	1	3	4
Total number of bleeds	1	4	5
Range of bleedings	0 ; 1	0 ; 2	0 ; 2
Mean bleedings per patient	0.067	0.267	0.333
Mean observation period (days)	837.5	837.5	837.5
Total observation period (years)	34.4	34.4	34.4
Poisson analysis*			
Annualised bleeding rate	0.029	0.116	0.145
95% CI	NA	0.042 ; 0.323	0.064 ; 0.329

CI: Confidence interval, NA: Not applicable.
* A 95% CI for the annualised bleeding rate is estimated from a Poisson analysis with over-dispersion if the number of bleeds is greater than 1, otherwise only the Poisson estimate is provided assuming no over-dispersion.

Annualised bleeding rate by age - full analysis set

	Treatment requiring	Non Treatment requiring	All
Elderly>65 years			
Number of patients with bleed	1	0	1
Total number of bleeds	1	0	1
Range of bleedings	0 ; 1	0 ; 0	0 ; 1
Mean bleedings per patient	0.500	0.000	0.500
Mean observation period (days)	714.5	714.5	714.5
Total observation period (years)	3.9	3.9	3.9
Poisson analysis*			
Annualised bleeding rate	0.256	0.000	0.256
95% CI	NA	NA	NA

CI: Confidence interval, NA: Not applicable.
* A 95% CI for the annualised bleeding rate is estimated from a Poisson analysis with over-dispersion if the number of bleeds is greater than 1, otherwise only the Poisson estimate is provided assuming no over-dispersion.

14.2.15 Annualised bleeding rate of all bleeding episodes for previously rFXIII untreated patients - Full analysis set

	Treatment requiring	Non Treatment requiring	All
Number of patients	5	5	5
Number of patients with bleed	3	2	4
Total number of bleeds	4	9	13
Range of bleedings	0 ; 2	0 ; 8	0 ; 10
Mean bleedings per patient	0.800	1.800	2.600
Mean observation period (days)	1072.3	1072.3	1072.3
Total observation period (years)	14.7	14.7	14.7
Poisson analysis*			
Annualised bleeding rate	0.204	0.613	0.818
95% CI	0.081 ; 0.516	0.167 ; 2.247	0.259 ; 2.582

* A 95% CI for the annualised bleeding rate is estimated from a Poisson analysis with over-dispersion if the number of bleeds is greater than 1, otherwise only the Poisson estimate is provided assuming no over-dispersion.

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14.3 Safety data

14.3.1 Displays of adverse events

14.3.1.1 Overview of adverse events - safety analysis set

	Children < 18 years N (%) E [R]	Adults (18 - 65 years) N (%) E [R]	Elderly > 65 years N (%) E [R]	Total N (%) E [R]
Number of patients	13	15	2	30
Total time in study (years)	37.00	34.44	3.92	75.36
Total number of exposure days	431	404	53	888
All adverse events	9 (69.2) 16 [0.43]	7 (46.7) 23 [0.67]	2 (100.0) 5 [1.28]	18 (60.0) 44 [0.58]
Serious adverse events	2 (15.4) 2 [0.05]	4 (26.7) 7 [0.20]	1 (50.0) 1 [0.26]	7 (23.3) 10 [0.13]
Adverse events by severity				
Mild	7 (53.8) 12 [0.32]	5 (33.3) 16 [0.46]	1 (50.0) 2 [0.51]	13 (43.3) 30 [0.40]
Moderate	3 (23.1) 4 [0.11]	5 (33.3) 6 [0.17]	2 (100.0) 3 [0.77]	10 (33.3) 13 [0.17]
Severe	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Adverse events by relationship				
Probably or possibly related	2 (15.4) 3 [0.08]	3 (20.0) 5 [0.15]	2 (100.0) 3 [0.77]	7 (23.3) 11 [0.15]
Unlikely related	7 (53.8) 13 [0.35]	6 (40.0) 18 [0.52]	2 (100.0) 2 [0.51]	15 (50.0) 33 [0.44]
Adverse events				
Leading to withdrawal	-	-	-	-

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

14.3.1.2 Specific adverse drug reactions - safety analysis set

	Children < 18 years N (%) E [R]	Adults (18 - 65 years) N (%) E [R]	Elderly > 65 years N (%) E [R]	Total N (%) E [R]
Number of patients	13	15	2	30
Total time in study (years)	37.00	34.44	3.92	75.36
Total number of exposure days	431	404	53	888
Any specific adverse drug reactions	2 (15.4) 3 [0.08]	-	-	2 (6.7) 3 [0.04]
Specific adverse drug reaction				
Anti-FXIII antibody	1 (7.7) 2 [0.05]	-	-	1 (3.3) 2 [0.03]
Lack of therapeutic effect	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]

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

14.3.1.3 Specific adverse drug reactions in previously rFXIII untreated patients - safety analysis set

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There is no data to display
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14.3.1.4 Adverse drug reactions - safety analysis set

	Children < 18 years N (%) E [R]	Adults (18 - 65 years) N (%) E [R]	Elderly > 65 years N (%) E [R]	Total N (%) E [R]
Number of patients	13	15	2	30
Total time in study (years)	37.00	34.44	3.92	75.36
Total number of exposure days	431	404	53	888
All adverse drug reactions	2 (15.4) 3 [0.08]	-	-	2 (6.7) 3 [0.04]
General disorders and administration site conditions	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Therapeutic response decreased	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Investigations	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Non-neutralising antibodies positive	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Musculoskeletal and connective tissue disorders	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Pain in extremity	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]

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

14.3.1.5 Adverse events - safety analysis set

	Children < 18 years N (%) E [R]	Adults (18 - 65 years) N (%) E [R]	Elderly > 65 years N (%) E [R]	Total N (%) E [R]
Number of patients	13	15	2	30
Total time in study (years)	37.00	34.44	3.92	75.36
Total number of exposure days	431	404	53	888
All adverse events	9 (69.2) 16 [0.43]	7 (46.7) 23 [0.67]	2 (100.0) 5 [1.28]	18 (60.0) 44 [0.58]
Infections and infestations	3 (23.1) 4 [0.11]	4 (26.7) 7 [0.20]	-	7 (23.3) 11 [0.15]
Nasopharyngitis	2 (15.4) 2 [0.05]	1 (6.7) 1 [0.03]	-	3 (10.0) 3 [0.04]
Sepsis	-	1 (6.7) 2 [0.06]	-	1 (3.3) 2 [0.03]
Conjunctivitis	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Gastroenteritis viral	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Influenza	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Sialoadenitis	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Tonsillitis	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Upper respiratory tract infection	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Nervous system disorders	1 (7.7) 2 [0.05]	2 (13.3) 3 [0.09]	1 (50.0) 2 [0.51]	4 (13.3) 7 [0.09]
Dizziness	-	1 (6.7) 2 [0.06]	1 (50.0) 1 [0.26]	2 (6.7) 3 [0.04]
Post-traumatic headache	1 (7.7) 2 [0.05]	-	-	1 (3.3) 2 [0.03]
Dysarthria	-	-	1 (50.0) 1 [0.26]	1 (3.3) 1 [0.01]
Headache	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
General disorders and administration site conditions	1 (7.7) 1 [0.03]	2 (13.3) 4 [0.12]	1 (50.0) 1 [0.26]	4 (13.3) 6 [0.08]
Chest discomfort	-	1 (6.7) 3 [0.09]	-	1 (3.3) 3 [0.04]
Fatigue	-	-	1 (50.0) 1 [0.26]	1 (3.3) 1 [0.01]
Influenza like illness	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Therapeutic response decreased	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]

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

Adverse events - safety analysis set

Continued...

	Children < 18 years N (%) E [R]	Adults (18 - 65 years) N (%) E [R]	Elderly > 65 years N (%) E [R]	Total N (%) E [R]
Injury, poisoning and procedural complications	3 (23.1) 4 [0.11]	1 (6.7) 1 [0.03]	-	4 (13.3) 5 [0.07]
Contusion	1 (7.7) 2 [0.05]	-	-	1 (3.3) 2 [0.03]
Accidental overdose	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Ligament sprain	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Limb injury	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Vascular disorders	1 (7.7) 1 [0.03]	1 (6.7) 2 [0.06]	1 (50.0) 1 [0.26]	3 (10.0) 4 [0.05]
Deep vein thrombosis	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Haematoma	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Hypertension	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Thrombophlebitis superficial	-	-	1 (50.0) 1 [0.26]	1 (3.3) 1 [0.01]
Musculoskeletal and connective tissue disorders	1 (7.7) 1 [0.03]	1 (6.7) 1 [0.03]	1 (50.0) 1 [0.26]	3 (10.0) 3 [0.04]
Arthralgia	-	-	1 (50.0) 1 [0.26]	1 (3.3) 1 [0.01]
Haemarthrosis	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Pain in extremity	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Gastrointestinal disorders	1 (7.7) 1 [0.03]	1 (6.7) 1 [0.03]	-	2 (6.7) 2 [0.03]
Abdominal pain	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Toothache	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Reproductive system and breast disorders	-	2 (13.3) 2 [0.06]	-	2 (6.7) 2 [0.03]
Ovarian rupture	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Prostatitis	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Hepatobiliary disorders	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Gallbladder polyp	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Investigations	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Non-neutralising antibodies positive	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]

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

Adverse events - safety analysis set

Continued...

	Children < 18 years N (%) E [R]	Adults (18 - 65 years) N (%) E [R]	Elderly > 65 years N (%) E [R]	Total N (%) E [R]
Psychiatric disorders	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Anxiety	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Skin and subcutaneous tissue disorders	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Eczema	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]

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

14.3.1.6 Adverse events with possible or probable relation to study product - safety analysis set

	Children < 18 years N (%) E [R]		Adults (18 - 65 years) N (%) E [R]		Elderly > 65 years N (%) E [R]		Total N (%) E [R]	
Number of patients	13		15		2		30	
Total time in study (years)	37.00		34.44		3.92		75.36	
Total number of exposure days	431		404		53		888	
All adverse events	2 (15.4)	3 [0.08]	3 (20.0)	5 [0.15]	2 (100.0)	3 [0.77]	7 (23.3)	11 [0.15]
General disorders and administration site conditions	1 (7.7)	1 [0.03]	1 (6.7)	3 [0.09]	1 (50.0)	1 [0.26]	3 (10.0)	5 [0.07]
Chest discomfort	-		1 (6.7)	3 [0.09]	-		1 (3.3)	3 [0.04]
Fatigue	-		-		1 (50.0)	1 [0.26]	1 (3.3)	1 [0.01]
Therapeutic response decreased	1 (7.7)	1 [0.03]	-		-		1 (3.3)	1 [0.01]
Nervous system disorders	-		2 (13.3)	2 [0.06]	1 (50.0)	1 [0.26]	3 (10.0)	3 [0.04]
Dizziness	-		1 (6.7)	1 [0.03]	1 (50.0)	1 [0.26]	2 (6.7)	2 [0.03]
Headache	-		1 (6.7)	1 [0.03]	-		1 (3.3)	1 [0.01]
Investigations	1 (7.7)	1 [0.03]	-		-		1 (3.3)	1 [0.01]
Non-neutralising antibodies positive	1 (7.7)	1 [0.03]	-		-		1 (3.3)	1 [0.01]
Musculoskeletal and connective tissue disorders	1 (7.7)	1 [0.03]	-		-		1 (3.3)	1 [0.01]
Pain in extremity	1 (7.7)	1 [0.03]	-		-		1 (3.3)	1 [0.01]
Vascular disorders	-		-		1 (50.0)	1 [0.26]	1 (3.3)	1 [0.01]
Thrombophlebitis superficial	-		-		1 (50.0)	1 [0.26]	1 (3.3)	1 [0.01]

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

14.3.1.7 Severe adverse events - safety analysis set

	Children < 18 years N (%) E [R]	Adults (18 - 65 years) N (%) E [R]	Elderly > 65 years N (%) E [R]	Total N (%) E [R]
Number of patients	13	15	2	30
Total time in study (years)	37.00	34.44	3.92	75.36
Total number of exposure days	431	404	53	888
All adverse events	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Infections and infestations	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Sepsis	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]

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

14.3.1.8 Moderate adverse events - safety analysis set

	Children < 18 years N (%) E [R]		Adults (18 - 65 years) N (%) E [R]		Elderly > 65 years N (%) E [R]		Total N (%) E [R]	
Number of patients	13		15		2		30	
Total time in study (years)	37.00		34.44		3.92		75.36	
Total number of exposure days	431		404		53		888	
All adverse events	3 (23.1)	4 [0.11]	5 (33.3)	6 [0.17]	2 (100.0)	3 [0.77]	10 (33.3)	13 [0.17]
Infections and infestations	1 (7.7)	1 [0.03]	2 (13.3)	2 [0.06]	-		3 (10.0)	3 [0.04]
Influenza	-		1 (6.7)	1 [0.03]	-		1 (3.3)	1 [0.01]
Sepsis	-		1 (6.7)	1 [0.03]	-		1 (3.3)	1 [0.01]
Sialoadenitis	1 (7.7)	1 [0.03]	-		-		1 (3.3)	1 [0.01]
Nervous system disorders	1 (7.7)	2 [0.05]	-		1 (50.0)	1 [0.26]	2 (6.7)	3 [0.04]
Post-traumatic headache	1 (7.7)	2 [0.05]	-		-		1 (3.3)	2 [0.03]
Dysarthria	-		-		1 (50.0)	1 [0.26]	1 (3.3)	1 [0.01]
Musculoskeletal and connective tissue disorders	-		1 (6.7)	1 [0.03]	1 (50.0)	1 [0.26]	2 (6.7)	2 [0.03]
Arthralgia	-		-		1 (50.0)	1 [0.26]	1 (3.3)	1 [0.01]
Haemarthrosis	-		1 (6.7)	1 [0.03]	-		1 (3.3)	1 [0.01]
Reproductive system and breast disorders	-		2 (13.3)	2 [0.06]	-		2 (6.7)	2 [0.03]
Ovarian rupture	-		1 (6.7)	1 [0.03]	-		1 (3.3)	1 [0.01]
Prostatitis	-		1 (6.7)	1 [0.03]	-		1 (3.3)	1 [0.01]
General disorders and administration site conditions	-		1 (6.7)	1 [0.03]	-		1 (3.3)	1 [0.01]
Chest discomfort	-		1 (6.7)	1 [0.03]	-		1 (3.3)	1 [0.01]
Psychiatric disorders	1 (7.7)	1 [0.03]	-		-		1 (3.3)	1 [0.01]
Anxiety	1 (7.7)	1 [0.03]	-		-		1 (3.3)	1 [0.01]

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

Moderate adverse events - safety analysis set

Continued...

	Children < 18 years N (%) E [R]	Adults (18 - 65 years) N (%) E [R]	Elderly > 65 years N (%) E [R]	Total N (%) E [R]
Vascular disorders	-	-	1 (50.0) 1 [0.26]	1 (3.3) 1 [0.01]
Thrombophlebitis superficial	-	-	1 (50.0) 1 [0.26]	1 (3.3) 1 [0.01]

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

14.3.1.9 Mild adverse events - safety analysis set

	Children < 18 years N (%) E [R]	Adults (18 - 65 years) N (%) E [R]	Elderly > 65 years N (%) E [R]	Total N (%) E [R]
Number of patients	13	15	2	30
Total time in study (years)	37.00	34.44	3.92	75.36
Total number of exposure days	431	404	53	888
All adverse events	7 (53.8) 12 [0.32]	5 (33.3) 16 [0.46]	1 (50.0) 2 [0.51]	13 (43.3) 30 [0.40]
Infections and infestations	2 (15.4) 3 [0.08]	2 (13.3) 4 [0.12]	-	4 (13.3) 7 [0.09]
Nasopharyngitis	2 (15.4) 2 [0.05]	1 (6.7) 1 [0.03]	-	3 (10.0) 3 [0.04]
Conjunctivitis	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Gastroenteritis viral	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Tonsillitis	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Upper respiratory tract infection	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
General disorders and administration site conditions	1 (7.7) 1 [0.03]	2 (13.3) 3 [0.09]	1 (50.0) 1 [0.26]	4 (13.3) 5 [0.07]
Chest discomfort	-	1 (6.7) 2 [0.06]	-	1 (3.3) 2 [0.03]
Fatigue	-	-	1 (50.0) 1 [0.26]	1 (3.3) 1 [0.01]
Influenza like illness	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Therapeutic response decreased	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Injury, poisoning and procedural complications	3 (23.1) 4 [0.11]	1 (6.7) 1 [0.03]	-	4 (13.3) 5 [0.07]
Contusion	1 (7.7) 2 [0.05]	-	-	1 (3.3) 2 [0.03]
Accidental overdose	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Ligament sprain	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Limb injury	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Nervous system disorders	-	2 (13.3) 3 [0.09]	1 (50.0) 1 [0.26]	3 (10.0) 4 [0.05]
Dizziness	-	1 (6.7) 2 [0.06]	1 (50.0) 1 [0.26]	2 (6.7) 3 [0.04]
Headache	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]

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

Mild adverse events - safety analysis set

Continued...

	Children < 18 years N (%) E [R]	Adults (18 - 65 years) N (%) E [R]	Elderly > 65 years N (%) E [R]	Total N (%) E [R]
Vascular disorders	1 (7.7) 1 [0.03]	1 (6.7) 2 [0.06]	-	2 (6.7) 3 [0.04]
Deep vein thrombosis	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Haematoma	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Hypertension	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Gastrointestinal disorders	1 (7.7) 1 [0.03]	1 (6.7) 1 [0.03]	-	2 (6.7) 2 [0.03]
Abdominal pain	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Toothache	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Hepatobiliary disorders	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Gallbladder polyp	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Investigations	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Non-neutralising antibodies positive	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Musculoskeletal and connective tissue disorders	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Pain in extremity	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Skin and subcutaneous tissue disorders	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Eczema	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]

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

14.3.1.10 Serious adverse event - safety analysis set

	Children < 18 years N (%) E [R]	Adults (18 - 65 years) N (%) E [R]	Elderly > 65 years N (%) E [R]	Total N (%) E [R]
Number of patients	13	15	2	30
Total time in study (years)	37.00	34.44	3.92	75.36
Total number of exposure days	431	404	53	888
All adverse events	2 (15.4) 2 [0.05]	4 (26.7) 7 [0.20]	1 (50.0) 1 [0.26]	7 (23.3) 10 [0.13]
Infections and infestations	1 (7.7) 1 [0.03]	2 (13.3) 3 [0.09]	-	3 (10.0) 4 [0.05]
Sepsis	-	1 (6.7) 2 [0.06]	-	1 (3.3) 2 [0.03]
Influenza	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Sialoadenitis	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Musculoskeletal and connective tissue disorders	-	1 (6.7) 1 [0.03]	1 (50.0) 1 [0.26]	2 (6.7) 2 [0.03]
Arthralgia	-	-	1 (50.0) 1 [0.26]	1 (3.3) 1 [0.01]
Haemarthrosis	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Nervous system disorders	1 (7.7) 1 [0.03]	1 (6.7) 1 [0.03]	-	2 (6.7) 2 [0.03]
Dizziness	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Post-traumatic headache	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Reproductive system and breast disorders	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Ovarian rupture	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Vascular disorders	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Deep vein thrombosis	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]

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

14.3.1.11 Serious adverse events in previously rFXIII untreated patients- safety analysis set

	Children < 18 years N (%) E [R]	Adults (18 - 65 years) N (%) E [R]	Elderly > 65 years N (%) E [R]	Total N (%) E [R]
Number of patients	13	15	2	30
Total time in study (years)	37.00	34.44	3.92	75.36
Total number of exposure days	431	404	53	888
All adverse events	1 (7.7) 1 [0.03]	3 (20.0) 5 [0.15]	-	4 (13.3) 6 [0.08]
Nervous system disorders	1 (7.7) 1 [0.03]	1 (6.7) 1 [0.03]	-	2 (6.7) 2 [0.03]
Dizziness	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Post-traumatic headache	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Infections and infestations	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Influenza	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Musculoskeletal and connective tissue disorders	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Haemarthrosis	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Reproductive system and breast disorders	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Ovarian rupture	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Vascular disorders	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Deep vein thrombosis	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]

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

14.3.1.12 Serious adverse events with probable or possible relation to study product - safety analysis set

There is no data to display

14.3.1.13 Medical events of special interest - safety analysis set

	Children < 18 years N (%) E [R]	Adults (18 - 65 years) N (%) E [R]	Elderly > 65 years N (%) E [R]	Total N (%) E [R]
Number of patients	13	15	2	30
Total time in study (years)	37.00	34.44	3.92	75.36
Total number of exposure days	431	404	53	888
All adverse events	3 (23.1) 3 [0.08]	1 (6.7) 1 [0.03]	-	4 (13.3) 4 [0.05]
General disorders and administration site conditions	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Therapeutic response decreased	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Injury, poisoning and procedural complications	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Accidental overdose	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Investigations	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Non-neutralising antibodies positive	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Vascular disorders	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Deep vein thrombosis	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]

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

14.3.1.14 Medical events of special interest in previously rFXIII untreated patients - safety analysis set

	Children < 18 years N (%) E [R]	Adults (18 - 65 years) N (%) E [R]	Elderly > 65 years N (%) E [R]	Total N (%) E [R]
Number of patients	13	15	2	30
Total time in study (years)	37.00	34.44	3.92	75.36
Total number of exposure days	431	404	53	888
All adverse events	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Vascular disorders	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Deep vein thrombosis	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]

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

14.3.1.15 Linked adverse events - safety analysis set

	Children < 18 years N (%) E [R]	Adults (18 - 65 years) N (%) E [R]	Elderly > 65 years N (%) E [R]	Total N (%) E [R]
Number of patients	13	15	2	30
Total time in study (years)	37.00	34.44	3.92	75.36
Total number of exposure days	431	404	53	888
All adverse events	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Nervous system disorders	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]
Dizziness	-	1 (6.7) 1 [0.03]	-	1 (3.3) 1 [0.01]

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

14.3.1.16 Medication errors and near medication errors - safety analysis set

	Children < 18 years N (%) E [R]	Adults (18 - 65 years) N (%) E [R]	Elderly > 65 years N (%) E [R]	Total N (%) E [R]
Number of patients	13	15	2	30
Total time in study (years)	37.00	34.44	3.92	75.36
Total number of exposure days	431	404	53	888
All adverse events	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Injury, poisoning and procedural complications	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]
Accidental overdose	1 (7.7) 1 [0.03]	-	-	1 (3.3) 1 [0.01]

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

14.3.1.17 Medication errors and near medication errors in previously rFXIII untreated patients - safety analysis set

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

f13-3868/freeze_20191022_er - 22OCT2019 - t_1431_teae_prev/14310125_mederr_prev.txt

14.3.1.18 Non-treatment emergent adverse events - safety analysis set

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

f13-3868/freeze_20191022_er - 22OCT2019 - t_1431_teae/14310130_non_teae.txt

14.3.2 Listings of deaths, other serious and significant adverse events

14.3.2.1 Serious adverse events by patient - safety analysis set

Patient ID/ Age(yrs)/ Treatment	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)	AE no. of related diagnosis*	Serious/ Life**/ MESI (Yes/No)	Severity/ Relation-ship	Action/ Outcome
[redacted]										

ED is the number of exposure days before onset of event.
*If an AE is a symptom, the AE number of the related diagnosis is listed. Such symptom AEs are not included in summaries.
**Life: Indicated whether a serious AE is life-threatening or not(only for serious AEs)

Serious adverse events by patient - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	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)	AE no. of related diagnosis*	Serious/ Life**/ MESI (Yes/No)	Severity/ Relation- ship	Action/ Outcome
[redacted]										

ED is the number of exposure days before onset of event.
*If an AE is a symptom, the AE number of the related diagnosis is listed. Such symptom AEs are not included in summaries.
**Life: Indicated whether a serious AE is life-threatening or not(only for serious AEs)

14.3.2.2 Adverse events leading to withdrawal - safety analysis set

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

f13-3868/freeze_20191022_er - 22OCT2019 - l_1627_teae/14320020_tesae_with.txt

14.3.2.3 Adverse events leading to death - safety analysis set

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

f13-3868/freeze_20191022_er - 22OCT2019 - l_1627_teae/14320030_tesae_death.txt

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

Narrative cover page

This section contains narratives on: serious adverse events and medical events of special interest. There were no deaths, pregnancies and adverse events leading to withdrawals in this study.

Narratives on serious adverse events and medical events of special interest were extracted from the safety database (Global Safety, Novo Nordisk) on 05-Aug-2019.

Narratives are bookmarked by category:

- serious adverse events
- suspected unexpected serious adverse reactions
- medical events of special interest
- pregnancies
- deaths
- blinded case narrative line listing of un-blinded cases

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*:* 05-Aug-2019 for data from the safety database.

Subject ID	Case number	Reason(s) for narrative	Preferred term	Assigned treatment group	Actual treatment (if different from assigned)
[redacted]			Haemarthrosis	Not randomised	Not applicable
			Ovarian rupture	Not randomised	Not applicable
			Post-traumatic headache	Not randomised	Not applicable
			Dizziness	Not randomised	Not applicable
			Influenza	Not randomised	Not applicable
			Deep vein thrombosis	Not randomised	Not applicable
			Sialoadenitis	Not randomised	Not applicable
			Sepsis	Not randomised	Not applicable
			Sepsis	Not randomised	Not applicable
			Arthralgia	Not randomised	Not applicable

Report #: **NN1841-3868 SAE Narrative Line Listing** Date: 05-Aug-2019 13:46:41

Period: 01-Jan-1900 Through 10-Jul-2019

Ingredient: **CATRIDECACOG**

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]	Patient Outcome
Study ID: NN1841-3868 (**10**)								
[redacted]								

[3] Unlocked Case.

Report #: **NN1841-3868 SAE Narrative Line Listing** Date: 05-Aug-2019 13:46:41

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

[3] Unlocked Case.

Report #: **NN1841-3868 SAE Narrative Line Listing** Date: 05-Aug-2019 13:46:41

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

[3] Unlocked Case.

Report #: **NN1841-3868 SAE Narrative Line Listing** Date: 05-Aug-2019 13:46:41

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

[3] Unlocked Case.

Report #: **NN1841-3868 SAE Narrative Line Listing** Date: 05-Aug-2019 13:46:41

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

[3] Unlocked Case.

Report #: **NN1841-3868 SAE Narrative Line Listing** Date: 05-Aug-2019 13:46:41

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

[3] Unlocked Case.

Report #: **NN1841-3868 SAE Narrative Line Listing** Date: 05-Aug-2019 13:46:41

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

[3] Unlocked Case.

Report #: **NN1841-3868 SAE Narrative Line Listing** Date: 05-Aug-2019 13:46:41

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

[3] Unlocked Case.

Report #: **NN1841-3868 SAE Narrative Line Listing** Date: 05-Aug-2019 13:46:41

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

[3] Unlocked Case.

Report #: **NN1841-3868 SAE Narrative Line Listing** Date: 05-Aug-2019 13:46:41

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

[3] Unlocked Case.

Report #: **NN1841-3868 SAE Narrative Line Listing** Date: 05-Aug-2019 13:46:41

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

[3] Unlocked Case.

Report #: **NN1841-3868 SAE Narrative Line Listing** Date: 05-Aug-2019 13:46:41

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

[3] Unlocked Case.

Report #: **NN1841-3868 SAE Narrative Line Listing** Date: 05-Aug-2019 13:46:41

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

[3] Unlocked Case.

Report #: **NN1841-3868 SAE Narrative Line Listing** Date: 05-Aug-2019 13:46:41

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

[3] Unlocked Case.

Report #: **NN1841-3868 SAE Narrative Line Listing** Date: 05-Aug-2019 13:46:41

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

[3] Unlocked Case.

Report #: **NN1841-3868 SAE Narrative Line Listing** Date: 05-Aug-2019 13:46:41

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

[3] Unlocked Case.

Report #: **NN1841-3868 SAE Narrative Line Listing** Date: 05-Aug-2019 13:46:41

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

[3] Unlocked Case.

Report #: **NN1841-3868 SAE Narrative Line Listing** Date: 05-Aug-2019 13:46:41

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

[3] Unlocked Case.

Report #: **NN1841-3868 SUSAR Narrative Line Listing** Date: 05-Aug-2019 11:02:59

Period: 01-Jan-1900 Through 10-Jul-2019

Ingredient: **CATRIDECACOG**

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]	Patient Outcome
[redacted]								

Report #: **NN1841-3868 SUSAR Narrative Line Listing** Date: 05-Aug-2019 11:02:59

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

Report #: **NN1841-3868 SUSAR Narrative Line Listing** Date: 05-Aug-2019 11:02:59

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

Report #: **NN1841-3868 SUSAR Narrative Line Listing** Date: 05-Aug-2019 11:02:59

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

Report #: **NN1841-3868 SUSAR Narrative Line Listing** Date: 05-Aug-2019 11:02:59

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

Report #:

NN1841-3868 MESI/AESI Narrative Line Listing

Date: 05-Aug-2019 10:07:39

Period: 01-Jan-1900 Through 10-Jul-2019

Ingredient: **CATRIDECACOG**

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]	Patient Outcome
Study ID: NN1841-3868 (**4**)								
[redacted]								

Report #: **NN1841-3868 MESI/AESI Narrative Line Listing** Date: 05-Aug-2019 10:07:39

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

Report #:

NN1841-3868 MESI/AESI Narrative Line Listing

Date: 05-Aug-2019 10:07:39

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

Report #: **NN1841-3868 MESI/AESI Narrative Line Listing** Date: 05-Aug-2019 10:07:39

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

Report #:

NN1841-3868 MESI/AESI Narrative Line Listing

Date: 05-Aug-2019 10:07:39

Period: 01-Jan-1900 Through 10-Jul-2019

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Report #:

NN1841-3868 MESI/AESI Narrative Line Listing

Date: 05-Aug-2019 10:07:39

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

Report #:

NN1841-3868 MESI/AESI Narrative Line Listing

Date: 05-Aug-2019 10:07:39

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

Report #:

NN1841-3868 MESI/AESI Narrative Line Listing

Date: 05-Aug-2019 10:07:39

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
[redacted]								

Report #:

NN1841-3868 Pregnancy Narrative Line Listing

Date: 05-Aug-2019 10:08:24

Period: 01-Jan-1900 Through 10-Jul-2019

Ingredient: **CATRIDECACOG**

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]	Patient Outcome

No Data Found

Report #:

NN1841-3868 Fatal Cases Narrative Line Listing

Date: 17-Sep-2019 02:44:03

Period: 01-Jan-1900 Through 10-Jul-2019

Ingredient: **CATRIDECACOG**

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	[Preferred Term]	Patient Outcome

No Data Found

Report #: **NN1841-3868 Blinded case Narrative Line Listing of un-blinded cases** Date: 05-Aug-2019 10:59:49

Period: 01-Jan-1900 Through 10-Jul-2019

Ingredient: **CATRIDECACOG**

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]	Patient Outcome
[redacted]								

[3] Unlocked Case.

Report #: **NN1841-3868 Blinded case Narrative Line Listing of un-blinded cases** Date: 05-Aug-2019 10:59:49

Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
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Period: 01-Jan-1900 Through 10-Jul-2019

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]	Patient Outcome
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[3] Unlocked Case.

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[3] Unlocked Case.

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[redacted]								

[3] Unlocked Case.

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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]	Patient Outcome
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[redacted]								

[3] Unlocked Case.

14.3.4 Abnormal laboratory value listings (by patient)

14.3.4.1 Listing of laboratory reference ranges

Category	Parameter	Substance	LabID	Age range (years)	Reference range lower limit	Reference range upper limit	Analysis Unit
[redacted]							

14.3.4.2 Listing of limits of quantification

Laboratory parameter	LLOQ Threshold		LLOQ Unit		LLOQ Truncation Value	ULOQ Threshold	ULOQ Unit	ULOQ Truncation Value
	Original	Converted	Original	Converted				
FXIII activity	<10.0	<10.0	%	IU/ml	0.050	-	-	-
FXIII activity	<15	<15	%	IU/ml	0.075	-	-	-
FXIII activity	<4.000	<4.000	%	IU/ml	0.020	-	-	-
FXIII activity	<0.04	<0.04	10^3 arb. enh/L	IU/ml	0.020	-	-	-
FXIII activity	<0.04	<0.04	10^3 arb.enh/L	IU/ml	0.020	-	-	-
FXIII activity	<0.05	<0.05	10^3arb.enh	IU/ml	0.025	-	-	-
FXIII activity	<0.04	<0.04	10^3arb.enh/L	IU/ml	0.020	-	-	-
FXIII activity	<0.100	<0.100	IU/mL	IU/ml	0.050	-	-	-
FXIII activity	<0.20	<0.20	X10^3 arb.enh/l	IU/ml	0.100	-	-	-
FXIII activity	<0.04	<0.04	arb 10^3/L	IU/ml	0.020	-	-	-
FXIII activity	<0.04	<0.04	arb. 10^3/L	IU/ml	0.020	-	-	-
FXIII activity	<0.040	<0.040	arb. 10^3/L	IU/ml	0.020	-	-	-
FXIII activity (Berichrom test)	<0.100	<0.100	IU/mL	IU/ml	0.050	-	-	-

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

f13-3868/freeze_20191022_er - 22OCT2019 - l_1434_loq/14340020_loq.txt

14.3.4.3 Vital signs outside reference range - safety analysis set

Patient ID/ Age(yrs)/ Treatment	Parameter	Visit	Collection date	Result	Unit	Reference range	Flag*
[redacted]							

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

14.3.4.4 Factor XIII activity outside reference range - safety analysis set

Patient ID/ Age(yrs)/ Treatment	Laboratory parameter	Visit	Collection date	Original Result	Original Unit	Converted Result	Converted Unit	Reference range	Flag*	CS	AF
[redacted]											

It is judged by the investigator if values outside the reference range are clinically significant.
* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
CS: clinically significant, AF: analysis flag, ND: not done, NA: not applicable

Factor XIII activity outside reference range - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Laboratory parameter	Visit	Collection date	Original Result	Original Unit	Converted Result	Converted Unit	Reference range	Flag*	CS	AF
[redacted]											

It is judged by the investigator if values outside the reference range are clinically significant.
* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
CS: clinically significant, AF: analysis flag, ND: not done, NA: not applicable

Factor XIII activity outside reference range - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Laboratory parameter	Visit	Collection date	Original Result	Original Unit	Converted Result	Converted Unit	Reference range	Flag*	CS	AF
[redacted]											

It is judged by the investigator if values outside the reference range are clinically significant.
* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
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Factor XIII activity outside reference range - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Laboratory parameter	Visit	Collection date	Original Result	Original Unit	Converted Result	Converted Unit	Reference range	Flag*	CS	AF
[redacted]											

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Factor XIII activity outside reference range - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Laboratory parameter	Visit	Collection date	Original Result	Original Unit	Converted Result	Converted Unit	Reference range	Flag*	CS	AF
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Factor XIII activity outside reference range - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Laboratory parameter	Visit	Collection date	Original Result	Original Unit	Converted Result	Converted Unit	Reference range	Flag*	CS	AF
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Factor XIII activity outside reference range - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Laboratory parameter	Visit	Collection date	Original Result	Original Unit	Converted Result	Converted Unit	Reference range	Flag*	CS	AF
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CS: clinically significant, AF: analysis flag, ND: not done, NA: not applicable

Factor XIII activity outside reference range - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Laboratory parameter	Visit	Collection date	Original Result	Original Unit	Converted Result	Converted Unit	Reference range	Flag*	CS	AF
[redacted]											

It is judged by the investigator if values outside the reference range are clinically significant.
* Values above reference range are marked with 'H'. Values below reference range are marked with 'L'.
CS: clinically significant, AF: analysis flag, ND: not done, NA: not applicable

14.3.5 Laboratory value displays

14.3.5.1 Factor XIII activity(IU/ml) - by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Visit 1 screening				
N	3	4		7
Mean (SD)	0.04 (0.028)	0.21 (0.242)		0.14 (0.194)
Median	0.04	0.11		0.07
Min ; Max	0.02 ; 0.08	0.06 ; 0.57		0.02 ; 0.57
Visit 2				
N	6	10	1	17
Mean (SD)	0.12 (0.079)	0.16 (0.112)	0.06 (-)	0.14 (0.100)
Median	0.13	0.15	0.06	0.12
Min ; Max	0.02 ; 0.23	0.02 ; 0.36	0.06 ; 0.06	0.02 ; 0.36
Change (SD)	0.03 (0.058)	-0.08 (0.264)	- (-)	-0.04 (0.214)
Visit 2, 1 month				
N	7	7	1	15
Mean (SD)	0.19 (0.175)	0.12 (0.067)	0.08 (-)	0.15 (0.129)
Median	0.18	0.13	0.08	0.13
Min ; Max	0.03 ; 0.51	0.05 ; 0.19	0.08 ; 0.08	0.03 ; 0.51
Change (SD)	0.11 (0.171)	0.03 (0.036)	- (-)	0.06 (0.100)
Visit 2, 2 months				
N	5	8		13
Mean (SD)	0.16 (0.121)	0.22 (0.168)		0.20 (0.149)
Median	0.18	0.20		0.18
Min ; Max	0.03 ; 0.32	0.06 ; 0.59		0.03 ; 0.59
Change (SD)	-0.01 (-)	-0.04 (0.197)		-0.03 (0.172)
Visit 2, 3 months				
N	7	6		13
Mean (SD)	0.17 (0.086)	0.12 (0.057)		0.14 (0.076)
Median	0.16	0.09		0.15
Min ; Max	0.05 ; 0.32	0.06 ; 0.20		0.05 ; 0.32
Change (SD)	0.07 (-)	0.02 (0.026)		0.03 (0.033)
Visit 2, 4 months				
N	4	8		12
Mean (SD)	0.12 (0.049)	0.12 (0.102)		0.12 (0.085)
Median	0.14	0.09		0.11
Min ; Max	0.05 ; 0.15	0.03 ; 0.35		0.03 ; 0.35
Change (SD)	0.01 (-)	0.00 (0.020)		0.00 (0.017)
Visit 2, 5 months				
N	4	6		10
Mean (SD)	0.14 (0.044)	0.12 (0.059)		0.13 (0.052)
Median	0.14	0.14		0.14
Min ; Max	0.09 ; 0.19	0.02 ; 0.19		0.02 ; 0.19
Change (SD)	- (-)	0.03 (0.035)		0.03 (0.035)
Visit 2, 6 months				
N	3	4		7
Mean (SD)	0.17 (0.115)	0.12 (0.060)		0.14 (0.084)
Median	0.17	0.11		0.16
Min ; Max	0.06 ; 0.29	0.06 ; 0.18		0.06 ; 0.29
Change (SD)	0.02 (-)	0.04 (0.039)		0.04 (0.034)
Visit 2, 7 months				
N	2	5		7
Mean (SD)	0.24 (0.152)	0.11 (0.070)		0.15 (0.104)
Median	0.24	0.13		0.13
Min ; Max	0.13 ; 0.35	0.02 ; 0.18		0.02 ; 0.35
Change (SD)	- (-)	0.04 (0.052)		0.04 (0.052)

Factor XIII activity(IU/ml) - by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 8 months				
N	3	4		7
Mean (SD)	0.09 (0.033)	0.10 (0.068)		0.09 (0.052)
Median	0.11	0.09		0.11
Min ; Max	0.05 ; 0.11	0.03 ; 0.18		0.03 ; 0.18
Change (SD)	- (-)	-0.12 (0.286)		-0.12 (0.286)
Visit 2, 9 months				
N	2	4		6
Mean (SD)	0.11 (0.081)	0.15 (0.073)		0.14 (0.071)
Median	0.11	0.16		0.14
Min ; Max	0.05 ; 0.16	0.06 ; 0.22		0.05 ; 0.22
Change (SD)	- (-)	0.04 (0.036)		0.04 (0.036)
Visit 2, 10 months				
N	2	2		4
Mean (SD)	0.17 (0.205)	0.13 (0.072)		0.15 (0.127)
Median	0.17	0.13		0.13
Min ; Max	0.02 ; 0.31	0.08 ; 0.18		0.02 ; 0.31
Change (SD)	- (-)	0.03 (0.008)		0.03 (0.008)
Visit 2, 11 months				
N	2	4		6
Mean (SD)	0.04 (0.028)	0.11 (0.055)		0.09 (0.058)
Median	0.04	0.10		0.07
Min ; Max	0.02 ; 0.06	0.06 ; 0.19		0.02 ; 0.19
Change (SD)	- (-)	0.03 (0.028)		0.03 (0.028)
Visit 2, 12 months				
N	1	3		4
Mean (SD)	0.05 (-)	0.16 (0.069)		0.13 (0.078)
Median	0.05	0.19		0.13
Min ; Max	0.05 ; 0.05	0.08 ; 0.21		0.05 ; 0.21
Change (SD)	- (-)	0.03 (0.013)		0.03 (0.013)
Visit 2, 13 months				
N	3	3		6
Mean (SD)	0.10 (0.034)	0.13 (0.047)		0.12 (0.042)
Median	0.11	0.16		0.12
Min ; Max	0.06 ; 0.13	0.08 ; 0.16		0.06 ; 0.16
Change (SD)	- (-)	0.02 (0.005)		0.02 (0.005)
Visit 2, 14 months				
N	3	3		6
Mean (SD)	0.07 (0.016)	0.13 (0.082)		0.10 (0.063)
Median	0.07	0.15		0.08
Min ; Max	0.05 ; 0.08	0.04 ; 0.20		0.04 ; 0.20
Change (SD)	- (-)	0.02 (0.049)		0.02 (0.049)
Visit 2, 15 months				
N	1	3		4
Mean (SD)	0.06 (-)	0.12 (0.075)		0.11 (0.069)
Median	0.06	0.10		0.08
Min ; Max	0.06 ; 0.06	0.06 ; 0.21		0.06 ; 0.21
Change (SD)	- (-)	0.05 (0.011)		0.05 (0.011)
Visit 2, 16 months				
N	2	3		5
Mean (SD)	0.19 (0.163)	0.13 (0.066)		0.15 (0.099)
Median	0.19	0.12		0.12
Min ; Max	0.07 ; 0.30	0.07 ; 0.20		0.07 ; 0.30
Change (SD)	- (-)	0.03 (0.028)		0.03 (0.028)

Factor XIII activity(IU/ml) - by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 17 months				
N	1	2		3
Mean (SD)	0.07 (-)	0.15 (0.105)		0.13 (0.088)
Median	0.07	0.15		0.08
Min ; Max	0.07 ; 0.07	0.08 ; 0.23		0.07 ; 0.23
Change (SD)	- (-)	0.05 (0.041)		0.05 (0.041)
Visit 2, 18 months				
N	1	2		3
Mean (SD)	0.02 (-)	0.11 (0.087)		0.08 (0.081)
Median	0.02	0.11		0.05
Min ; Max	0.02 ; 0.02	0.05 ; 0.17		0.02 ; 0.17
Change (SD)	- (-)	0.01 (0.023)		0.01 (0.023)
Visit 2, 19 months				
N	3	2		5
Mean (SD)	0.17 (0.125)	0.14 (0.110)		0.16 (0.106)
Median	0.17	0.14		0.17
Min ; Max	0.05 ; 0.30	0.06 ; 0.22		0.05 ; 0.30
Change (SD)	- (-)	0.03 (0.046)		0.03 (0.046)
Visit 2, 20 months				
N	1	2		3
Mean (SD)	0.05 (-)	0.12 (0.103)		0.10 (0.084)
Median	0.05	0.12		0.05
Min ; Max	0.05 ; 0.05	0.05 ; 0.20		0.05 ; 0.20
Change (SD)	- (-)	0.02 (0.040)		0.02 (0.040)
Visit 2, 21 months				
N	1	3		4
Mean (SD)	0.05 (-)	0.14 (0.102)		0.11 (0.094)
Median	0.05	0.11		0.08
Min ; Max	0.05 ; 0.05	0.05 ; 0.25		0.05 ; 0.25
Change (SD)	- (-)	0.04 (0.077)		0.04 (0.077)
Visit 2, 22 months				
N	1	2		3
Mean (SD)	0.05 (-)	0.13 (0.120)		0.10 (0.095)
Median	0.05	0.13		0.05
Min ; Max	0.05 ; 0.05	0.04 ; 0.21		0.04 ; 0.21
Change (SD)	- (-)	-0.02 (-)		-0.02 (-)
Visit 2, 23 months				
N	1	1		2
Mean (SD)	0.06 (-)	0.03 (-)		0.05 (0.021)
Median	0.06	0.03		0.05
Min ; Max	0.06 ; 0.06	0.03 ; 0.03		0.03 ; 0.06
Change (SD)	- (-)	-0.03 (-)		-0.03 (-)
Visit 2, 24 months				
N	1	1		2
Mean (SD)	0.06 (-)	0.04 (-)		0.05 (0.014)
Median	0.06	0.04		0.05
Min ; Max	0.06 ; 0.06	0.04 ; 0.04		0.04 ; 0.06
Change (SD)	- (-)	-0.02 (-)		-0.02 (-)
Visit 2, 25 months				
N	1	1		2
Mean (SD)	0.04 (-)	0.04 (-)		0.04 (0.000)
Median	0.04	0.04		0.04
Min ; Max	0.04 ; 0.04	0.04 ; 0.04		0.04 ; 0.04
Change (SD)	- (-)	-0.02 (-)		-0.02 (-)

Factor XIII activity(IU/ml) - by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 26 months				
N	1	1		2
Mean (SD)	0.05 (-)	0.06 (-)		0.06 (0.007)
Median	0.05	0.06		0.06
Min ; Max	0.05 ; 0.05	0.06 ; 0.06		0.05 ; 0.06
Change (SD)	- (-)	0.00 (-)		0.00 (-)
Visit 2, 27 months				
N	2	1		3
Mean (SD)	0.13 (0.148)	0.05 (-)		0.10 (0.114)
Median	0.13	0.05		0.05
Min ; Max	0.02 ; 0.23	0.05 ; 0.05		0.02 ; 0.23
Change (SD)	- (-)	-0.01 (-)		-0.01 (-)
Visit 2, 28 months				
N	2	1		3
Mean (SD)	0.23 (0.247)	0.06 (-)		0.17 (0.199)
Median	0.23	0.06		0.06
Min ; Max	0.05 ; 0.40	0.06 ; 0.06		0.05 ; 0.40
Change (SD)	- (-)	0.00 (-)		0.00 (-)
Visit 2, 29 months				
N	1	2		3
Mean (SD)	0.05 (-)	0.24 (0.219)		0.17 (0.188)
Median	0.05	0.24		0.08
Min ; Max	0.05 ; 0.05	0.08 ; 0.39		0.05 ; 0.39
Change (SD)	- (-)	-0.08 (0.141)		-0.08 (0.141)
Visit 2, 30 months				
N	1	1		2
Mean (SD)	0.08 (-)	0.05 (-)		0.07 (0.021)
Median	0.08	0.05		0.07
Min ; Max	0.08 ; 0.08	0.05 ; 0.05		0.05 ; 0.08
Change (SD)	- (-)	-0.01 (-)		-0.01 (-)
Visit 2, 31 months				
N	1	1		2
Mean (SD)	0.06 (-)	0.07 (-)		0.07 (0.007)
Median	0.06	0.07		0.07
Min ; Max	0.06 ; 0.06	0.07 ; 0.07		0.06 ; 0.07
Change (SD)	- (-)	0.01 (-)		0.01 (-)
Visit 2, 32 months				
N	1	1		2
Mean (SD)	0.02 (-)	0.09 (-)		0.06 (0.049)
Median	0.02	0.09		0.06
Min ; Max	0.02 ; 0.02	0.09 ; 0.09		0.02 ; 0.09
Change (SD)	- (-)	0.03 (-)		0.03 (-)
Visit 2, 33 months				
N	1	1		2
Mean (SD)	0.08 (-)	0.06 (-)		0.07 (0.014)
Median	0.08	0.06		0.07
Min ; Max	0.08 ; 0.08	0.06 ; 0.06		0.06 ; 0.08
Change (SD)	- (-)	0.00 (-)		0.00 (-)
Visit 2, 34 months				
N	1	1		2
Mean (SD)	0.07 (-)	0.05 (-)		0.06 (0.014)
Median	0.07	0.05		0.06
Min ; Max	0.07 ; 0.07	0.05 ; 0.05		0.05 ; 0.07
Change (SD)	- (-)	-0.01 (-)		-0.01 (-)

Factor XIII activity(IU/ml) - by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 35 months				
N	1	1		2
Mean (SD)	0.05 (-)	0.05 (-)		0.05 (0.000)
Median	0.05	0.05		0.05
Min ; Max	0.05 ; 0.05	0.05 ; 0.05		0.05 ; 0.05
Change (SD)	- (-)	-0.01 (-)		-0.01 (-)
Visit 2, 36 months				
N	1	1		2
Mean (SD)	0.08 (-)	0.04 (-)		0.06 (0.028)
Median	0.08	0.04		0.06
Min ; Max	0.08 ; 0.08	0.04 ; 0.04		0.04 ; 0.08
Change (SD)	- (-)	-0.02 (-)		-0.02 (-)
Visit 2, 37 months				
N	1	1		2
Mean (SD)	0.08 (-)	0.07 (-)		0.08 (0.007)
Median	0.08	0.07		0.08
Min ; Max	0.08 ; 0.08	0.07 ; 0.07		0.07 ; 0.08
Change (SD)	- (-)	0.01 (-)		0.01 (-)
Visit 2, 38 months				
N	1	1		2
Mean (SD)	0.09 (-)	0.05 (-)		0.07 (0.028)
Median	0.09	0.05		0.07
Min ; Max	0.09 ; 0.09	0.05 ; 0.05		0.05 ; 0.09
Change (SD)	- (-)	-0.01 (-)		-0.01 (-)
Visit 2, 39 months				
N	1	1		2
Mean (SD)	0.09 (-)	0.07 (-)		0.08 (0.014)
Median	0.09	0.07		0.08
Min ; Max	0.09 ; 0.09	0.07 ; 0.07		0.07 ; 0.09
Change (SD)	- (-)	0.01 (-)		0.01 (-)
Visit 2, 40 months				
N	1	1		2
Mean (SD)	0.06 (-)	0.09 (-)		0.08 (0.021)
Median	0.06	0.09		0.08
Min ; Max	0.06 ; 0.06	0.09 ; 0.09		0.06 ; 0.09
Change (SD)	- (-)	0.03 (-)		0.03 (-)
Visit 2, 41 months				
N	1	1		2
Mean (SD)	0.06 (-)	0.06 (-)		0.06 (0.000)
Median	0.06	0.06		0.06
Min ; Max	0.06 ; 0.06	0.06 ; 0.06		0.06 ; 0.06
Change (SD)	- (-)	0.00 (-)		0.00 (-)
Visit 2, 42 months				
N	1	1		2
Mean (SD)	0.08 (-)	0.09 (-)		0.09 (0.007)
Median	0.08	0.09		0.09
Min ; Max	0.08 ; 0.08	0.09 ; 0.09		0.08 ; 0.09
Change (SD)	- (-)	0.03 (-)		0.03 (-)
Visit 2, 43 months				
N	1	1		2
Mean (SD)	0.08 (-)	0.07 (-)		0.08 (0.007)
Median	0.08	0.07		0.08
Min ; Max	0.08 ; 0.08	0.07 ; 0.07		0.07 ; 0.08
Change (SD)	- (-)	0.01 (-)		0.01 (-)

Factor XIII activity(IU/ml) - by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 44 months				
N	1	1		2
Mean (SD)	0.07 (-)	0.06 (-)		0.07 (0.007)
Median	0.07	0.06		0.07
Min ; Max	0.07 ; 0.07	0.06 ; 0.06		0.06 ; 0.07
Change (SD)	- (-)	0.00 (-)		0.00 (-)
Visit 2, 45 months				
N	1	1		2
Mean (SD)	0.07 (-)	0.05 (-)		0.06 (0.014)
Median	0.07	0.05		0.06
Min ; Max	0.07 ; 0.07	0.05 ; 0.05		0.05 ; 0.07
Change (SD)	- (-)	-0.01 (-)		-0.01 (-)
Visit 2, 46 months				
N	1	1		2
Mean (SD)	0.10 (-)	0.06 (-)		0.08 (0.028)
Median	0.10	0.06		0.08
Min ; Max	0.10 ; 0.10	0.06 ; 0.06		0.06 ; 0.10
Change (SD)	- (-)	0.00 (-)		0.00 (-)
Visit 2, 47 months				
N	1	1		2
Mean (SD)	0.15 (-)	0.06 (-)		0.11 (0.064)
Median	0.15	0.06		0.11
Min ; Max	0.15 ; 0.15	0.06 ; 0.06		0.06 ; 0.15
Change (SD)	- (-)	0.00 (-)		0.00 (-)
Visit 2, 48 months				
N	1	1		2
Mean (SD)	0.10 (-)	0.07 (-)		0.09 (0.021)
Median	0.10	0.07		0.09
Min ; Max	0.10 ; 0.10	0.07 ; 0.07		0.07 ; 0.10
Change (SD)	- (-)	0.01 (-)		0.01 (-)
Visit 2, 49 months				
N	1			1
Mean (SD)	0.08 (-)			0.08 (-)
Median	0.08			0.08
Min ; Max	0.08 ; 0.08			0.08 ; 0.08
Change (SD)	- (-)			- (-)
Visit 2, 50 months				
N	1			1
Mean (SD)	0.08 (-)			0.08 (-)
Median	0.08			0.08
Min ; Max	0.08 ; 0.08			0.08 ; 0.08
Change (SD)	- (-)			- (-)
Visit 2, 51 months				
N	1			1
Mean (SD)	0.06 (-)			0.06 (-)
Median	0.06			0.06
Min ; Max	0.06 ; 0.06			0.06 ; 0.06
Change (SD)	- (-)			- (-)
Visit 2, 52 months				
N	1			1
Mean (SD)	0.07 (-)			0.07 (-)
Median	0.07			0.07
Min ; Max	0.07 ; 0.07			0.07 ; 0.07
Change (SD)	- (-)			- (-)

Factor XIII activity(IU/ml) - by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 53 months				
N	1			1
Mean (SD)	0.12 (-)			0.12 (-)
Median	0.12			0.12
Min ; Max	0.12 ; 0.12			0.12 ; 0.12
Change (SD)	- (-)			- (-)
Visit 2, 54 months				
N	1			1
Mean (SD)	0.09 (-)			0.09 (-)
Median	0.09			0.09
Min ; Max	0.09 ; 0.09			0.09 ; 0.09
Change (SD)	- (-)			- (-)
Visit 2, 55 months				
N	1			1
Mean (SD)	0.09 (-)			0.09 (-)
Median	0.09			0.09
Min ; Max	0.09 ; 0.09			0.09 ; 0.09
Change (SD)	- (-)			- (-)
Visit 2, 56 months				
N	1			1
Mean (SD)	0.07 (-)			0.07 (-)
Median	0.07			0.07
Min ; Max	0.07 ; 0.07			0.07 ; 0.07
Change (SD)	- (-)			- (-)
Visit 2, 57 months				
N	1			1
Mean (SD)	0.07 (-)			0.07 (-)
Median	0.07			0.07
Min ; Max	0.07 ; 0.07			0.07 ; 0.07
Change (SD)	- (-)			- (-)
Visit 2, 58 months				
N	1			1
Mean (SD)	0.09 (-)			0.09 (-)
Median	0.09			0.09
Min ; Max	0.09 ; 0.09			0.09 ; 0.09
Change (SD)	- (-)			- (-)
Visit 2, 59 months				
N	1			1
Mean (SD)	1.02 (-)			1.02 (-)
Median	1.02			1.02
Min ; Max	1.02 ; 1.02			1.02 ; 1.02
Change (SD)	- (-)			- (-)
Visit 2, 60 months				
N	1			1
Mean (SD)	0.09 (-)			0.09 (-)
Median	0.09			0.09
Min ; Max	0.09 ; 0.09			0.09 ; 0.09
Change (SD)	- (-)			- (-)
Visit 2, 61 months				
N	1			1
Mean (SD)	0.06 (-)			0.06 (-)
Median	0.06			0.06
Min ; Max	0.06 ; 0.06			0.06 ; 0.06
Change (SD)	- (-)			- (-)

Factor XIII activity(IU/ml) - by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 62 months				
N	1			1
Mean (SD)	0.09 (-)			0.09 (-)
Median	0.09			0.09
Min ; Max	0.09 ; 0.09			0.09 ; 0.09
Change (SD)	- (-)			- (-)
Visit 2, 63 months				
N	1			1
Mean (SD)	0.12 (-)			0.12 (-)
Median	0.12			0.12
Min ; Max	0.12 ; 0.12			0.12 ; 0.12
Change (SD)	- (-)			- (-)
Visit 2, 64 months				
N	1			1
Mean (SD)	0.08 (-)			0.08 (-)
Median	0.08			0.08
Min ; Max	0.08 ; 0.08			0.08 ; 0.08
Change (SD)	- (-)			- (-)
Visit 2, 65 months				
N	1			1
Mean (SD)	0.07 (-)			0.07 (-)
Median	0.07			0.07
Min ; Max	0.07 ; 0.07			0.07 ; 0.07
Change (SD)	- (-)			- (-)
Visit 2, 66 months				
N	1			1
Mean (SD)	0.07 (-)			0.07 (-)
Median	0.07			0.07
Min ; Max	0.07 ; 0.07			0.07 ; 0.07
Change (SD)	- (-)			- (-)
Visit 2, 67 months				
N	1			1
Mean (SD)	0.10 (-)			0.10 (-)
Median	0.10			0.10
Min ; Max	0.10 ; 0.10			0.10 ; 0.10
Change (SD)	- (-)			- (-)
Visit 2, 68 months				
N	1			1
Mean (SD)	0.11 (-)			0.11 (-)
Median	0.11			0.11
Min ; Max	0.11 ; 0.11			0.11 ; 0.11
Change (SD)	- (-)			- (-)
End of study				
N	5	4		9
Mean (SD)	0.11 (0.037)	0.11 (0.070)		0.11 (0.050)
Median	0.11	0.10		0.11
Min ; Max	0.07 ; 0.15	0.05 ; 0.21		0.05 ; 0.21
Change (SD)	0.03 (-)	0.03 (0.049)		0.03 (0.035)

14.3.5.2 FXIII activity (Berichrom FXIII test IU/mL) - by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Visit 1 screening				
N	8	12	2	22
Mean (SD)	0.17 (0.053)	0.28 (0.257)	0.17 (0.071)	0.23 (0.197)
Median	0.16	0.17	0.17	0.16
Min ; Max	0.11 ; 0.27	0.05 ; 0.90	0.12 ; 0.22	0.05 ; 0.90
Visit 2				
N	5	5		10
Mean (SD)	0.17 (0.073)	0.22 (0.142)		0.19 (0.109)
Median	0.14	0.15		0.15
Min ; Max	0.12 ; 0.30	0.05 ; 0.37		0.05 ; 0.37
Change (SD)	-0.01 (0.055)	-0.12 (0.157)		-0.07 (0.129)
Visit 2, 1 month				
N	3	3	2	8
Mean (SD)	0.37 (0.176)	0.12 (0.071)	0.23 (0.042)	0.24 (0.158)
Median	0.44	0.11	0.23	0.20
Min ; Max	0.18 ; 0.51	0.05 ; 0.19	0.20 ; 0.26	0.05 ; 0.51
Change (SD)	0.20 (0.178)	-0.22 (0.367)	0.06 (0.028)	0.01 (0.296)
Visit 2, 2 months				
N	5	2		7
Mean (SD)	0.22 (0.071)	0.44 (0.216)		0.28 (0.152)
Median	0.18	0.44		0.26
Min ; Max	0.15 ; 0.32	0.29 ; 0.59		0.15 ; 0.59
Change (SD)	0.03 (0.065)	0.03 (0.175)		0.03 (0.089)
Visit 2, 3 months				
N	4	1	1	6
Mean (SD)	0.23 (0.083)	0.17 (-)	0.32 (-)	0.24 (0.079)
Median	0.23	0.17	0.32	0.23
Min ; Max	0.16 ; 0.32	0.17 ; 0.17	0.32 ; 0.32	0.16 ; 0.32
Change (SD)	0.03 (0.077)	0.03 (-)	0.10 (-)	0.04 (0.065)
Visit 2, 4 months				
N	3	1		4
Mean (SD)	0.13 (0.017)	0.14 (-)		0.13 (0.015)
Median	0.13	0.14		0.13
Min ; Max	0.12 ; 0.15	0.14 ; 0.14		0.12 ; 0.15
Change (SD)	-0.09 (-)	0.09 (-)		0.00 (0.124)
Visit 2, 5 months				
N	2		1	3
Mean (SD)	0.22 (0.033)		0.29 (-)	0.24 (0.049)
Median	0.22		0.29	0.24
Min ; Max	0.19 ; 0.24		0.29 ; 0.29	0.19 ; 0.29
Change (SD)	0.05 (0.095)		0.07 (-)	0.06 (0.068)
Visit 2, 6 months				
N	2	1		3
Mean (SD)	0.17 (0.167)	0.17 (-)		0.17 (0.118)
Median	0.17	0.17		0.17
Min ; Max	0.05 ; 0.29	0.17 ; 0.17		0.05 ; 0.29
Change (SD)	-0.02 (0.127)	0.12 (-)		0.03 (0.120)

The FXIII activity assay used at the central laboratory is the Berichrom ® assay.
f13-3868/freeze_20191022_er - 22OCT2019 - t_1435_lab/14350901200_rfxiii_act.txt

FXIII activity (Berichrom FXIII test IU/mL) - by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 7 months				
N	2			2
Mean (SD)	0.26 (0.117)			0.26 (0.117)
Median	0.26			0.26
Min ; Max	0.18 ; 0.35			0.18 ; 0.35
Change (SD)	0.09 (0.055)			0.09 (0.055)
Visit 2, 8 months				
N	3			3
Mean (SD)	0.13 (0.012)			0.13 (0.012)
Median	0.13			0.13
Min ; Max	0.12 ; 0.14			0.12 ; 0.14
Change (SD)	0.02 (-)			0.02 (-)
Visit 2, 9 months				
N	2			2
Mean (SD)	0.20 (0.078)			0.20 (0.078)
Median	0.20			0.20
Min ; Max	0.15 ; 0.26			0.15 ; 0.26
Change (SD)	0.00 (0.028)			0.00 (0.028)
Visit 2, 10 months				
N	3			3
Mean (SD)	0.20 (0.059)			0.20 (0.059)
Median	0.18			0.18
Min ; Max	0.15 ; 0.26			0.15 ; 0.26
Change (SD)	0.01 (0.018)			0.01 (0.018)
Visit 2, 11 months				
N	1	3		4
Mean (SD)	0.11 (-)	0.16 (0.035)		0.15 (0.039)
Median	0.11	0.15		0.15
Min ; Max	0.11 ; 0.11	0.14 ; 0.20		0.11 ; 0.20
Change (SD)	-0.01 (-)	-0.21 (0.427)		-0.16 (0.362)
Visit 2, 12 months				
N	1			1
Mean (SD)	0.16 (-)			0.16 (-)
Median	0.16			0.16
Min ; Max	0.16 ; 0.16			0.16 ; 0.16
Change (SD)	0.03 (-)			0.03 (-)
Visit 2, 13 months				
N	2			2
Mean (SD)	0.12 (0.011)			0.12 (0.011)
Median	0.12			0.12
Min ; Max	0.11 ; 0.12			0.11 ; 0.12
Change (SD)	- (-)			- (-)
Visit 2, 15 months				
N	2	1		3
Mean (SD)	0.16 (0.042)	0.12 (-)		0.14 (0.037)
Median	0.16	0.12		0.13
Min ; Max	0.13 ; 0.19	0.12 ; 0.12		0.12 ; 0.19
Change (SD)	-0.04 (0.063)	0.07 (-)		-0.00 (0.078)
Visit 2, 19 months				
N	3			3
Mean (SD)	0.10 (0.040)			0.10 (0.040)
Median	0.11			0.11
Min ; Max	0.05 ; 0.12			0.05 ; 0.12
Change (SD)	0.00 (-)			0.00 (-)

The FXIII activity assay used at the central laboratory is the Berichrom ® assay.
f13-3868/freeze_20191022_er - 22OCT2019 - t_1435_lab/14350901200_rfxiii_act.txt

FXIII activity (Berichrom FXIII test IU/mL) - by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 25 months				
N	3			3
Mean (SD)	0.15 (0.036)			0.15 (0.036)
Median	0.14			0.14
Min ; Max	0.12 ; 0.19			0.12 ; 0.19
Change (SD)	-0.01 (-)			-0.01 (-)
Visit 2, 26 months				
N	2			2
Mean (SD)	0.20 (0.006)			0.20 (0.006)
Median	0.20			0.20
Min ; Max	0.20 ; 0.21			0.20 ; 0.21
Change (SD)	- (-)			- (-)
Visit 2, 27 months				
N	2			2
Mean (SD)	0.23 (0.123)			0.23 (0.123)
Median	0.23			0.23
Min ; Max	0.15 ; 0.32			0.15 ; 0.32
Change (SD)	0.05 (-)			0.05 (-)
Visit 2, 28 months				
N	2			2
Mean (SD)	0.33 (0.172)			0.33 (0.172)
Median	0.33			0.33
Min ; Max	0.21 ; 0.45			0.21 ; 0.45
Change (SD)	0.18 (-)			0.18 (-)
Visit 2, 30 months				
N	1			1
Mean (SD)	0.13 (-)			0.13 (-)
Median	0.13			0.13
Min ; Max	0.13 ; 0.13			0.13 ; 0.13
Change (SD)	0.00 (-)			0.00 (-)
End of study				
N	5	3	1	9
Mean (SD)	0.15 (0.121)	0.17 (0.166)	0.31 (-)	0.18 (0.129)
Median	0.12	0.11	0.31	0.12
Min ; Max	0.05 ; 0.36	0.05 ; 0.36	0.31 ; 0.31	0.05 ; 0.36
Change (SD)	0.06 (0.194)	-0.04 (0.126)	0.09 (-)	0.02 (0.132)

The FXIII activity assay used at the central laboratory is the Berichrom ® assay.

14.3.5.3 Anti rFXIII antibodies by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Visit 1 screening, N (%)				
N	8 (100.0)	12 (100.0)	2 (100.0)	22 (100.0)
Negative	7 (87.5)	12 (100.0)	2 (100.0)	21 (95.5)
Positive	1 (12.5)	-	-	1 (4.5)
Visit 2, N (%)				
N	5 (100.0)	5 (100.0)	-	10 (100.0)
Negative	4 (80.0)	5 (100.0)	-	9 (90.0)
Positive	1 (20.0)	-	-	1 (10.0)
Visit 2, 1 month, N (%)				
N	3 (100.0)	3 (100.0)	2 (100.0)	8 (100.0)
Negative	3 (100.0)	3 (100.0)	2 (100.0)	8 (100.0)
Visit 2, 2 months, N (%)				
N	5 (100.0)	2 (100.0)	-	7 (100.0)
Negative	5 (100.0)	2 (100.0)	-	7 (100.0)
Visit 2, 3 months, N (%)				
N	4 (100.0)	1 (100.0)	1 (100.0)	6 (100.0)
Negative	4 (100.0)	1 (100.0)	1 (100.0)	6 (100.0)
Visit 2, 4 months, N (%)				
N	3 (100.0)	1 (100.0)	-	4 (100.0)
Negative	3 (100.0)	1 (100.0)	-	4 (100.0)
Visit 2, 5 months, N (%)				
N	2 (100.0)	-	1 (100.0)	3 (100.0)
Negative	2 (100.0)	-	1 (100.0)	3 (100.0)
Visit 2, 6 months, N (%)				
N	2 (100.0)	1 (100.0)	-	3 (100.0)
Negative	2 (100.0)	1 (100.0)	-	3 (100.0)
Visit 2, 7 months, N (%)				
N	2 (100.0)	-	-	2 (100.0)
Negative	2 (100.0)	-	-	2 (100.0)
Visit 2, 8 months, N (%)				
N	3 (100.0)	-	-	3 (100.0)
Negative	3 (100.0)	-	-	3 (100.0)
Visit 2, 9 months, N (%)				
N	2 (100.0)	1 (100.0)	-	3 (100.0)
Negative	2 (100.0)	1 (100.0)	-	3 (100.0)
Visit 2, 10 months, N (%)				
N	3 (100.0)	-	-	3 (100.0)
Negative	3 (100.0)	-	-	3 (100.0)
Visit 2, 11 months, N (%)				
N	1 (100.0)	3 (100.0)	-	4 (100.0)
Negative	1 (100.0)	3 (100.0)	-	4 (100.0)
Visit 2, 12 months, N (%)				
N	1 (100.0)	-	-	1 (100.0)
Negative	1 (100.0)	-	-	1 (100.0)
Visit 2, 13 months, N (%)				
N	2 (100.0)	-	-	2 (100.0)
Negative	2 (100.0)	-	-	2 (100.0)

Anti rFXIII antibodies by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 15 months, N (%)				
N	2 (100.0)	1 (100.0)	-	3 (100.0)
Negative	2 (100.0)	1 (100.0)	-	3 (100.0)
Visit 2, 19 months, N (%)				
N	3 (100.0)	-	-	3 (100.0)
Negative	3 (100.0)	-	-	3 (100.0)
Visit 2, 25 months, N (%)				
N	3 (100.0)	-	-	3 (100.0)
Negative	3 (100.0)	-	-	3 (100.0)
Visit 2, 26 months, N (%)				
N	2 (100.0)	-	-	2 (100.0)
Negative	2 (100.0)	-	-	2 (100.0)
Visit 2, 27 months, N (%)				
N	2 (100.0)	-	-	2 (100.0)
Negative	2 (100.0)	-	-	2 (100.0)
Visit 2, 28 months, N (%)				
N	2 (100.0)	-	-	2 (100.0)
Negative	2 (100.0)	-	-	2 (100.0)
Visit 2, 30 months, N (%)				
N	1 (100.0)	-	-	1 (100.0)
Negative	1 (100.0)	-	-	1 (100.0)
End of study, N (%)				
N	5 (100.0)	3 (100.0)	1 (100.0)	9 (100.0)
Negative	5 (100.0)	3 (100.0)	1 (100.0)	9 (100.0)

f13-3868/freeze_20191022_er - 22OCT2019 - t_1435_labchar/14350901300_rfxiii_anti.txt

14.3.5.4 rFXIII antibodies (titre) by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Visit 2, N (%)				
N	1 (100.0)	-	-	1 (100.0)
1	1 (100.0)	-	-	1 (100.0)

f13-3868/freeze_20191022_er - 22OCT2019 - t_1435_labchar/14350901400_rfxiii_anti_tit.txt

14.3.5.5 rFXIII neutralizing antibodies by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Visit 1 screening, N (%)				
N	1 (100.0)	-	-	1 (100.0)
Negative	1 (100.0)	-	-	1 (100.0)
Visit 2, N (%)				
N	1 (100.0)	-	-	1 (100.0)
Negative	1 (100.0)	-	-	1 (100.0)

f13-3868/freeze_20191022_er - 22OCT2019 - t_1435_labchar/14350901500_rfxiii_neu.txt

14.3.5.6 FXIII activity (Berichrom FXIII test IU/mL) - safety analysis set

Patient	Number of samples	Mean value (IU/mL)
[redacted]		

Sorted according to ascending FXIII activity value.
* The total mean value is calculated as the mean of the individual patient mean values.

f13-3868/freeze_20191022_er - 22OCT2019 - t_1435_lab_mean/14350901900_rfxiii_act_mean.txt

14.3.6 Other safety observations displays

14.3.6.1 Pulse (Beats/Min) by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Visit 1 screening				
N	11	13	2	26
Mean (SD)	84.5 (10.9)	78.2 (11.4)	67.5 (4.9)	80.0 (11.6)
Median	84.0	75.0	67.5	76.5
Min ; Max	66.0 ; 101.0	63.0 ; 105.0	64.0 ; 71.0	63.0 ; 105.0
EOT				
N	9	7	1	17
Mean (SD)	84.8 (20.7)	79.1 (12.9)	77.0 (-)	82.0 (16.9)
Median	84.0	81.0	77.0	81.0
Min ; Max	53.0 ; 109.0	60.0 ; 99.0	77.0 ; 77.0	53.0 ; 109.0

EOT: End of study.

f13-3868/freeze_20191022_er - 22OCT2019 - t_1436_vital/14360010_pulse.txt

14.3.6.2 Systolic blood pressure (mmHg) by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Visit 1 screening				
N	10	13	2	25
Mean (SD)	104.2 (10.0)	123.3 (15.9)	141.0 (15.6)	117.1 (17.7)
Median	103.5	120.0	141.0	117.0
Min ; Max	91.0 ; 120.0	100.0 ; 157.0	130.0 ; 152.0	91.0 ; 157.0
EOT				
N	8	7	1	16
Mean (SD)	105.3 (12.0)	127.4 (14.5)	136.0 (-)	116.9 (17.3)
Median	104.0	122.0	136.0	119.5
Min ; Max	90.0 ; 123.0	112.0 ; 155.0	136.0 ; 136.0	90.0 ; 155.0

EOT: End of study.

f13-3868/freeze_20191022_er - 22OCT2019 - t_1436_vital/14360020_sys.txt

14.3.6.3 Diastolic blood pressure (mmHg) by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Visit 1 screening				
N	10	13	2	25
Mean (SD)	60.2 (6.8)	76.8 (11.2)	78.0 (2.8)	70.3 (12.3)
Median	60.0	74.0	78.0	72.0
Min ; Max	53.0 ; 75.0	60.0 ; 105.0	76.0 ; 80.0	53.0 ; 105.0
EOT				
N	8	7	1	16
Mean (SD)	63.4 (12.1)	81.7 (12.4)	91.0 (-)	73.1 (15.4)
Median	66.0	80.0	91.0	71.5
Min ; Max	44.0 ; 80.0	68.0 ; 105.0	91.0 ; 91.0	44.0 ; 105.0

EOT: End of study.

f13-3868/freeze_20191022_er - 22OCT2019 - t_1436_vital/14360030_dia.txt

14.3.6.4 Body measurements - weight (kg) by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Visit 1 screening				
N	13	14	[redacted]2	29
Mean (SD)	35.0 (19.1)	84.5 (20.7)	[redacted]	63.0 (32.0)
Median	34.1	83.0	[redacted]	64.2
Min ; Max	12.0 ; 64.2	52.5 ; 127.0	[redacted]	12.0 ; 127.0
Visit 2				
N	10	12	[redacted]2	24
Mean (SD)	29.6 (16.6)	84.6 (15.3)	[redacted](1.5)	62.6 (32.2)
Median	23.4	82.6	[redacted]	73.9
Min ; Max	12.5 ; 57.9	56.0 ; 114.9	[redacted]	12.5 ; 114.9
Change (SD)	1.2 (1.7)	0.0 (3.3)	0.4 (0.6)	0.6 (2.5)
Visit 2, 1 month				
N	11	11	[redacted]2	24
Mean (SD)	33.6 (18.5)	81.8 (18.6)	[redacted](0.3)	60.7 (30.9)
Median	24.6	78.0	[redacted]	61.4
Min ; Max	13.5 ; 65.4	52.0 ; 117.0	[redacted]	13.5 ; 117.0
Change (SD)	1.9 (1.7)	-0.6 (1.8)	-1.4 (0.6)	0.5 (2.1)
Visit 2, 2 months				
N	8	9	[redacted]1	18
Mean (SD)	29.6 (14.5)	82.3 (25.1)	[redacted] (-)	59.5 (33.8)
Median	24.1	77.4	[redacted]	56.3
Min ; Max	13.0 ; 57.5	51.8 ; 122.0	[redacted]	13.0 ; 122.0
Change (SD)	2.3 (1.8)	-0.4 (2.5)	-2.4 (-)	0.7 (2.6)
Visit 2, 3 months				
N	9	7	[redacted]1	17
Mean (SD)	34.0 (17.6)	83.9 (19.6)	[redacted] (-)	57.6 (31.1)
Median	24.7	78.0	[redacted]	57.7
Min ; Max	13.0 ; 63.9	55.0 ; 116.5	[redacted]	13.0 ; 116.5
Change (SD)	4.0 (4.1)	-0.0 (2.1)	-8.2 (-)	1.6 (4.5)
Visit 2, 4 months				
N	8	8	[redacted]1	17
Mean (SD)	39.5 (18.7)	84.0 (26.0)	[redacted] (-)	63.5 (31.5)
Median	39.9	77.3	[redacted]	57.8
Min ; Max	13.4 ; 67.7	50.0 ; 123.0	[redacted]	13.4 ; 123.0
Change (SD)	2.4 (2.2)	-1.0 (1.9)	-3.8 (-)	0.5 (2.8)
Visit 2, 5 months				
N	7	6	[redacted]1	14
Mean (SD)	35.4 (20.2)	84.3 (22.6)	[redacted] (-)	60.5 (32.7)
Median	25.0	78.9	[redacted]	62.9
Min ; Max	13.4 ; 67.8	55.0 ; 121.0	[redacted]	13.4 ; 121.0
Change (SD)	2.3 (1.4)	-1.3 (2.7)	-1.6 (-)	0.5 (2.7)
Visit 2, 6 months				
N	7	6	[redacted]1	14
Mean (SD)	32.7 (15.3)	85.2 (21.9)	[redacted] (-)	59.6 (32.8)
Median	25.2	79.0	[redacted]	58.6
Min ; Max	13.7 ; 58.1	59.0 ; 122.0	[redacted]	13.7 ; 122.0
Change (SD)	3.5 (2.8)	-0.4 (2.4)	-0.7 (-)	1.5 (3.2)

EOT: End of study.

Body measurements - weight (kg) by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 7 months				
N	7	6		13
Mean (SD)	33.6 (15.1)	84.9 (21.8)		57.2 (32.0)
Median	27.3	79.1		57.4
Min ; Max	13.8 ; 57.4	58.0 ; 121.0		13.8 ; 121.0
Change (SD)	4.4 (3.8)	-0.7 (2.7)		2.1 (4.2)
Visit 2, 8 months				
N	5	4		9
Mean (SD)	32.8 (16.9)	92.5 (21.1)		59.3 (36.1)
Median	25.8	88.0		57.7
Min ; Max	14.2 ; 57.7	74.0 ; 120.0		14.2 ; 120.0
Change (SD)	3.2 (2.8)	-1.7 (3.6)		1.0 (3.9)
Visit 2, 9 months				
N	5	5		10
Mean (SD)	32.9 (17.2)	86.3 (24.2)		59.6 (34.4)
Median	26.4	78.0		59.0
Min ; Max	14.5 ; 58.5	59.5 ; 121.8		14.5 ; 121.8
Change (SD)	3.3 (2.6)	-0.6 (2.8)		1.3 (3.3)
Visit 2, 10 months				
N	5	4		9
Mean (SD)	33.6 (17.4)	91.5 (20.5)		59.3 (35.2)
Median	26.5	86.5		58.4
Min ; Max	15.0 ; 58.4	74.0 ; 119.0		15.0 ; 119.0
Change (SD)	4.0 (3.6)	-2.7 (3.9)		1.0 (5.0)
Visit 2, 11 months				
N	5	6		11
Mean (SD)	33.1 (17.2)	84.1 (22.0)		60.9 (32.7)
Median	26.7	78.8		58.5
Min ; Max	15.3 ; 58.5	58.0 ; 123.0		15.3 ; 123.0
Change (SD)	3.5 (3.1)	-1.5 (2.9)		0.8 (3.9)
Visit 2, 12 months				
N	5	4		9
Mean (SD)	33.6 (16.8)	84.3 (29.8)		56.1 (34.4)
Median	27.2	76.0		58.0
Min ; Max	15.2 ; 58.2	58.0 ; 127.0		15.2 ; 127.0
Change (SD)	4.1 (3.0)	0.2 (0.9)		2.3 (3.0)
Visit 2, 13 months				
N	7	4		11
Mean (SD)	40.3 (18.6)	82.8 (28.5)		55.8 (30.1)
Median	43.1	76.0		56.0
Min ; Max	15.8 ; 66.0	56.0 ; 123.0		15.8 ; 123.0
Change (SD)	3.3 (3.0)	-1.3 (2.1)		1.6 (3.5)
Visit 2, 14 months				
N	5	4		9
Mean (SD)	34.3 (17.0)	82.5 (28.8)		55.7 (33.2)
Median	26.8	76.0		55.0
Min ; Max	16.5 ; 59.0	55.0 ; 123.0		16.5 ; 123.0
Change (SD)	4.7 (3.2)	-1.6 (2.2)		1.9 (4.2)

EOT: End of study.

Body measurements - weight (kg) by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 15 months				
N	4	5		9
Mean (SD)	39.7 (16.0)	82.1 (24.7)		63.3 (30.0)
Median	36.5	78.0		59.4
Min ; Max	26.4 ; 59.4	56.0 ; 123.0		26.4 ; 123.0
Change (SD)	5.7 (4.5)	-0.9 (2.0)		2.0 (4.7)
Visit 2, 16 months				
N	3	4		7
Mean (SD)	37.4 (18.6)	83.5 (29.1)		63.7 (33.9)
Median	[illegible]	76.0		58.8
Min ; Max	[illegible]	57.0 ; 125.0		25.9 ; 125.0
Change (SD)	3.5 (2.6)	-0.6 (1.3)		1.2 (2.8)
Visit 2, 17 months				
N	3	3		6
Mean (SD)	37.8 (18.6)	92.3 (28.4)		65.1 (36.8)
Median	[illegible]	[illegible]		66.6
Min ; Max	[illegible]	[illegible]		26.9 ; 125.0
Change (SD)	3.8 (2.3)	-0.6 (1.6)		1.6 (3.0)
Visit 2, 18 months				
N	4	3		7
Mean (SD)	44.9 (20.5)	93.0 (29.5)		65.5 (34.1)
Median	44.7	[illegible]		63.3
Min ; Max	26.9 ; 63.3	[illegible]		26.9 ; 127.0
Change (SD)	3.4 (2.9)	0.1 (1.1)		2.0 (2.8)
Visit 2, 19 months				
N	5	3		8
Mean (SD)	45.3 (17.2)	94.0 (31.2)		63.6 (32.9)
Median	46.4	[illegible]		62.2
Min ; Max	27.2 ; 62.5	[illegible]		27.2 ; 130.0
Change (SD)	2.6 (3.7)	1.1 (2.0)		2.0 (3.1)
Visit 2, 20 months				
N	3	2		5
Mean (SD)	39.6 (20.5)	[illegible] (1.4)		54.6 (25.1)
Median	[illegible]	[illegible]		63.3
Min ; Max	[illegible]	[illegible]		27.1 ; 78.0
Change (SD)	5.7 (0.4)	1.1 (3.0)		3.8 (2.9)
Visit 2, 21 months				
N	3	3		6
Mean (SD)	40.4 (20.4)	78.3 (2.5)		59.4 (24.5)
Median	[illegible]	[illegible]		70.0
Min ; Max	[illegible]	[illegible]		27.4 ; 81.0
Change (SD)	6.5 (1.0)	1.4 (2.2)		4.0 (3.2)
Visit 2, 22 months				
N	3	3		6
Mean (SD)	41.7 (21.4)	95.3 (29.3)		68.5 (37.3)
Median	[illegible]	[illegible]		71.2
Min ; Max	[illegible]	[illegible]		27.7 ; 129.0
Change (SD)	7.8 (1.4)	2.4 (0.7)		5.1 (3.1)

EOT: End of study.

Body measurements - weight (kg) by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 23 months				
N	3	1		4
Mean (SD)	41.4 (21.7)	[redacted]		51.1 (26.2)
Median	[redacted]	[redacted]		48.2
Min ; Max	[redacted]	[redacted]		27.9 ; 80.0
Change (SD)	7.5 (1.0)	[redacted]		7.4 (0.8)
Visit 2, 24 months				
N	3	2		5
Mean (SD)	41.6 (21.9)	[redacted] (35.4)		67.8 (42.8)
Median	[redacted]	[redacted]		66.9
Min ; Max	[redacted]	[redacted]		28.0 ; 132.0
Change (SD)	7.7 (1.2)	7.1 (3.0)		7.5 (1.7)
Visit 2, 25 months				
N	5	2		7
Mean (SD)	47.1 (16.8)	[redacted] (34.6)		63.8 (34.7)
Median	46.9	[redacted]		63.8
Min ; Max	29.1 ; 64.0	[redacted]		29.1 ; 130.0
Change (SD)	4.4 (4.6)	5.6 (3.7)		4.7 (4.1)
Visit 2, 26 months				
N	5	2		7
Mean (SD)	47.2 (17.1)	[redacted] (36.4)		64.2 (35.5)
Median	45.2	[redacted]		64.4
Min ; Max	29.5 ; 65.1	[redacted]		29.5 ; 132.5
Change (SD)	4.5 (5.0)	6.9 (1.9)		5.2 (4.3)
Visit 2, 27 months				
N	4	2		6
Mean (SD)	47.6 (18.5)	[redacted] (38.9)		68.2 (39.1)
Median	48.1	[redacted]		63.5
Min ; Max	29.2 ; 65.1	[redacted]		29.2 ; 137.0
Change (SD)	6.1 (6.1)	9.6 (0.6)		7.3 (5.0)
Visit 2, 28 months				
N	4	1		5
Mean (SD)	48.0 (18.8)	[redacted]		55.0 (22.6)
Median	48.6	[redacted]		63.1
Min ; Max	29.4 ; 65.2	[redacted]		29.4 ; 83.0
Change (SD)	6.5 (5.4)	[redacted]		7.2 (5.0)
Visit 2, 29 months				
N	3	2		5
Mean (SD)	43.5 (18.8)	[redacted] (33.2)		68.7 (40.5)
Median	[redacted]	[redacted]		65.0
Min ; Max	[redacted]	[redacted]		29.8 ; 130.0
Change (SD)	9.6 (3.4)	6.6 (5.1)		8.4 (3.9)
Visit 2, 30 months				
N	3	2		5
Mean (SD)	43.1 (19.5)	[redacted] (30.4)		68.1 (39.9)
Median	[redacted]	[redacted]		65.4
Min ; Max	[redacted]	[redacted]		29.4 ; 127.0
Change (SD)	9.2 (2.6)	5.6 (7.9)		7.7 (4.8)

EOT: End of study.

Body measurements - weight (kg) by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 31 months				
N	3	2		5
Mean (SD)	43.4 (18.7)	[redacted] (31.8)		68.7 (40.3)
Median	[redacted]	[redacted]		65.0
Min ; Max	[redacted]	[redacted]		31.4 ; 129.0
Change (SD)	9.5 (2.3)	6.6 (6.5)		8.3 (4.0)
Visit 2, 32 months				
N	3	2		5
Mean (SD)	43.1 (18.5)	[redacted] (31.8)		68.5 (40.4)
Median	[redacted]	[redacted]		64.4
Min ; Max	[redacted]	[redacted]		31.7 ; 129.0
Change (SD)	9.2 (2.4)	6.6 (6.5)		8.1 (3.9)
Visit 2, 33 months				
N	2	2		4
Mean (SD)	[redacted] (23.4)	[redacted] (31.1)		76.9 (40.4)
Median	[redacted]	[redacted]		74.2
Min ; Max	[redacted]	[redacted]		31.3 ; 128.0
Change (SD)	8.1 (2.4)	6.1 (7.2)		7.1 (4.5)
Visit 2, 34 months				
N	2	2		4
Mean (SD)	[redacted] (24.3)	[redacted] (31.8)		78.5 (40.7)
Median	[redacted]	[redacted]		75.8
Min ; Max	[redacted]	[redacted]		32.3 ; 130.0
Change (SD)	9.7 (1.6)	7.6 (6.5)		8.7 (4.0)
Visit 2, 35 months				
N	2	2		4
Mean (SD)	[redacted] (24.3)	[redacted] (35.4)		79.7 (42.9)
Median	[redacted]	[redacted]		75.8
Min ; Max	[redacted]	[redacted]		32.2 ; 135.0
Change (SD)	9.6 (1.6)	10.1 (3.0)		9.9 (2.0)
Visit 2, 36 months				
N	1	2		3
Mean (SD)	[redacted]	[redacted] (33.2)		95.4 (35.2)
Median	[redacted]	[redacted]		[redacted]
Min ; Max	[redacted]	[redacted]		[redacted]
Change (SD)	[redacted]	10.6 (5.1)		9.4 (4.1)
Visit 2, 37 months				
N	1	1		2
Mean (SD)	[redacted]	[redacted]		[redacted] (15.8)
Median	[redacted]	[redacted]		[redacted]
Min ; Max	[redacted]	[redacted]		[redacted]
Change (SD)	[redacted]	[redacted]		10.5 (5.3)
Visit 2, 38 months				
N	1	1		2
Mean (SD)	[redacted]	[redacted]		[redacted] (15.9)
Median	[redacted]	[redacted]		[redacted]
Min ; Max	[redacted]	[redacted]		[redacted]
Change (SD)	[redacted]	[redacted]		10.4 (5.4)

EOT: End of study.

Body measurements - weight (kg) by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 39 months				
N	1	1		2
Mean (SD)	[redacted]	[redacted]		[redacted] (17.0)
Median				
Min ; Max				
Change (SD)				9.6 (6.5)
Visit 2, 40 months				
N	1	1		2
Mean (SD)	[redacted]	[redacted]		[redacted] (15.4)
Median				
Min ; Max				
Change (SD)				10.7 (4.9)
Visit 2, 41 months				
N	1	1		2
Mean (SD)	[redacted]	[redacted]		[redacted] (17.0)
Median				
Min ; Max				
Change (SD)				9.6 (6.5)
Visit 2, 42 months				
N	1	1		2
Mean (SD)	[redacted]	[redacted]		[redacted] (14.6)
Median				
Min ; Max				
Change (SD)				11.3 (4.1)
Visit 2, 43 months				
N	1	1		2
Mean (SD)	[redacted]	[redacted]		[redacted] (14.9)
Median				
Min ; Max				
Change (SD)				11.1 (4.5)
Visit 2, 44 months				
N	1	2		3
Mean (SD)	[redacted]	[redacted] (33.9)		96.6 (34.7)
Median				
Min ; Max				
Change (SD)		11.1 (4.4)		10.6 (3.2)
Visit 2, 45 months				
N	1	2		3
Mean (SD)	[redacted]	[redacted] (33.9)		96.4 (34.9)
Median				
Min ; Max				
Change (SD)		11.1 (4.4)		10.4 (3.3)
Visit 2, 46 months				
N	1	1		2
Mean (SD)	[redacted]	[redacted]		[redacted] (15.6)
Median				
Min ; Max				
Change (SD)				10.6 (5.1)

EOT: End of study.

Body measurements - weight (kg) by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 47 months				
N	1	1		2
Mean (SD)	[redacted]	[redacted]		[redacted] (13.8)
Median				
Min ; Max				
Change (SD)				11.9 (3.3)
Visit 2, 48 months				
N	1	1		2
Mean (SD)	[redacted]	[redacted]		[redacted] (13.4)
Median				
Min ; Max				
Change (SD)				12.1 (3.0)
Visit 2, 49 months				
N	1			1
Mean (SD)	[redacted]			[redacted]
Median				
Min ; Max				
Change (SD)				
Visit 2, 50 months				
N	1			1
Mean (SD)	[redacted]			[redacted]
Median				
Min ; Max				
Change (SD)				
Visit 2, 51 months				
N	1			1
Mean (SD)	[redacted]			[redacted]
Median				
Min ; Max				
Change (SD)				
Visit 2, 52 months				
N	1			1
Mean (SD)	[redacted]			[redacted]
Median				
Min ; Max				
Change (SD)				
Visit 2, 53 months				
N	1			1
Mean (SD)	[redacted]			[redacted]
Median				
Min ; Max				
Change (SD)				
Visit 2, 54 months				
N	1			1
Mean (SD)	[redacted]			[redacted]
Median				
Min ; Max				
Change (SD)				

EOT: End of study.

Body measurements - weight (kg) by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 55 months				
N	1			1
Mean (SD)	[redacted]			
Median				
Min ; Max				
Change (SD)				
Visit 2, 56 months				
N	1			1
Mean (SD)	[redacted]			
Median				
Min ; Max				
Change (SD)				
Visit 2, 57 months				
N	1			1
Mean (SD)	[redacted]			
Median				
Min ; Max				
Change (SD)				
Visit 2, 58 months				
N	1			1
Mean (SD)	[redacted]			
Median				
Min ; Max				
Change (SD)				
Visit 2, 60 months				
N	1			1
Mean (SD)	[redacted]			
Median				
Min ; Max				
Change (SD)				
Visit 2, 61 months				
N	1			1
Mean (SD)	[redacted]			
Median				
Min ; Max				
Change (SD)				
Visit 2, 62 months				
N	1			1
Mean (SD)	[redacted]			
Median				
Min ; Max				
Change (SD)				
Visit 2, 63 months				
N	1			1
Mean (SD)	[redacted]			
Median				
Min ; Max				
Change (SD)				

EOT: End of study.

Body measurements - weight (kg) by visit - safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 64 months				
N		1		1
Mean (SD)		[redacted]		
Median				
Min ; Max				
Change (SD)				
Visit 2, 65 months				
N		1		1
Mean (SD)		[redacted]		
Median				
Min ; Max				
Change (SD)				
Visit 2, 66 months				
N		1		1
Mean (SD)		[redacted]		
Median				
Min ; Max				
Change (SD)				
Visit 2, 67 months				
N		1		1
Mean (SD)		[redacted]		
Median				
Min ; Max				
Change (SD)				
Visit 2, 68 months				
N		1		1
Mean (SD)		[redacted]		
Median				
Min ; Max				
Change (SD)				
EOT				
N	9	9	1	19
Mean (SD)	41.5 (17.9)	88.5 (26.5)	[redacted]	66.5 (32.4)
Median	45.0	87.0		65.2
Min ; Max	17.0 ; 66.5	54.0 ; 135.0		17.0 ; 135.0
Change (SD)	7.0 (5.0)	5.0 (5.4)		5.6 (5.3)

EOT: End of study.

14.3.6.5 Body measurements - BMI (kg/m^2) by visit- safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Visit 1 screening				
N	13	12	2	27
Mean (SD)	17.7 (4.8)	29.3 (6.3)	[redacted] (1.2)	23.8 (8.0)
Median	15.5	29.4	[redacted]	22.7
Min ; Max	13.2 ; 27.7	20.8 ; 39.4	[redacted]	13.2 ; 39.4
Visit 2				
N	10	10	2	22
Mean (SD)	16.9 (4.0)	29.7 (6.1)	[redacted] (1.4)	24.0 (8.2)
Median	15.3	30.4	[redacted]	22.9
Min ; Max	13.4 ; 26.3	21.6 ; 39.7	[redacted]	13.4 ; 39.7
Change (SD)	0.8 (1.0)	0.2 (1.1)	0.2 (0.2)	0.4 (1.0)
Visit 2, 1 month				
N	11	9	2	22
Mean (SD)	18.1 (3.9)	29.1 (6.8)	[redacted] (1.0)	23.7 (7.6)
Median	16.4	27.3	[redacted]	22.4
Min ; Max	14.8 ; 26.8	20.6 ; 40.4	[redacted]	14.8 ; 40.4
Change (SD)	1.4 (1.3)	-0.2 (0.6)	-0.4 (0.2)	0.6 (1.3)
Visit 2, 2 months				
N	8	7	1	16
Mean (SD)	16.8 (2.1)	29.8 (8.0)	[redacted]	23.4 (8.6)
Median	16.4	33.8	[redacted]	20.8
Min ; Max	14.3 ; 21.0	20.5 ; 40.4	[redacted]	14.3 ; 40.4
Change (SD)	1.6 (1.4)	-0.2 (0.8)	[redacted]	0.6 (1.5)
Visit 2, 3 months				
N	9	6	1	16
Mean (SD)	18.7 (4.9)	30.5 (7.5)	[redacted]	23.7 (8.2)
Median	16.6	31.6	[redacted]	21.2
Min ; Max	14.3 ; 30.1	21.2 ; 40.3	[redacted]	14.3 ; 40.3
Change (SD)	2.5 (2.5)	0.1 (0.7)	[redacted]	1.3 (2.4)
Visit 2, 4 months				
N	8	7	1	16
Mean (SD)	18.2 (3.3)	29.8 (7.9)	[redacted]	24.0 (8.1)
Median	17.4	34.1	[redacted]	21.7
Min ; Max	14.7 ; 24.0	19.8 ; 39.7	[redacted]	14.7 ; 39.7
Change (SD)	1.3 (0.9)	-0.3 (0.6)	[redacted]	0.4 (1.1)
Visit 2, 5 months				
N	7	5	1	13
Mean (SD)	17.9 (3.4)	29.5 (6.8)	[redacted]	23.4 (7.7)
Median	16.6	33.5	[redacted]	21.2
Min ; Max	14.7 ; 24.0	21.2 ; 35.1	[redacted]	14.7 ; 35.1
Change (SD)	1.4 (0.8)	-0.5 (0.8)	[redacted]	0.5 (1.2)
Visit 2, 6 months				
N	7	5	1	13
Mean (SD)	17.5 (2.2)	29.9 (6.4)	[redacted]	23.3 (7.7)
Median	17.0	33.8	[redacted]	21.3
Min ; Max	15.0 ; 21.3	22.8 ; 35.1	[redacted]	15.0 ; 35.1
Change (SD)	2.1 (1.4)	-0.2 (0.8)	[redacted]	1.0 (1.6)

EOT: End of study.

Body measurements - BMI (kg/m^2) by visit- safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 7 months				
N	7	5		12
Mean (SD)	18.1 (2.3)	29.8 (6.4)		22.9 (7.4)
Median	17.4	33.5		20.6
Min ; Max	15.1 ; 21.0	22.4 ; 35.1		15.1 ; 35.1
Change (SD)	2.6 (2.0)	-0.3 (0.8)		1.4 (2.2)
Visit 2, 8 months				
N	5	4		9
Mean (SD)	17.7 (2.2)	31.5 (5.7)		23.8 (8.2)
Median	17.4	34.0		21.1
Min ; Max	15.6 ; 21.1	23.1 ; 35.1		15.6 ; 35.1
Change (SD)	2.0 (1.3)	-0.5 (1.1)		0.9 (1.7)
Visit 2, 9 months				
N	5	5		10
Mean (SD)	17.7 (2.2)	29.9 (6.3)		23.8 (7.8)
Median	16.7	33.7		22.2
Min ; Max	15.9 ; 21.4	23.0 ; 35.1		15.9 ; 35.1
Change (SD)	2.0 (1.3)	-0.1 (0.9)		1.0 (1.5)
Visit 2, 10 months				
N	5	4		9
Mean (SD)	18.1 (2.2)	31.2 (5.5)		23.9 (7.8)
Median	16.9	33.6		21.4
Min ; Max	16.4 ; 21.4	23.1 ; 34.7		16.4 ; 34.7
Change (SD)	2.4 (1.6)	-0.8 (1.1)		1.0 (2.2)
Visit 2, 11 months				
N	5	5		10
Mean (SD)	17.9 (2.2)	29.5 (6.2)		23.7 (7.5)
Median	16.8	33.0		21.9
Min ; Max	16.0 ; 21.4	22.4 ; 34.7		16.0 ; 34.7
Change (SD)	2.2 (1.7)	-0.6 (1.0)		0.8 (2.0)
Visit 2, 12 months				
N	5	4		9
Mean (SD)	18.3 (1.9)	28.9 (7.1)		23.0 (7.2)
Median	17.7	28.9		21.3
Min ; Max	16.7 ; 21.3	22.4 ; 35.2		16.7 ; 35.2
Change (SD)	2.6 (1.5)	0.1 (0.3)		1.5 (1.7)
Visit 2, 13 months				
N	7	4		11
Mean (SD)	19.1 (2.5)	28.4 (7.0)		22.5 (6.3)
Median	19.2	28.6		21.1
Min ; Max	16.2 ; 23.4	21.6 ; 34.7		16.2 ; 34.7
Change (SD)	2.0 (1.7)	-0.4 (0.6)		1.1 (1.8)
Visit 2, 14 months				
N	5	4		9
Mean (SD)	18.7 (1.9)	28.3 (7.1)		22.9 (6.8)
Median	18.1	28.6		21.2
Min ; Max	16.6 ; 21.6	21.2 ; 34.7		16.6 ; 34.7
Change (SD)	3.0 (1.8)	-0.5 (0.7)		1.4 (2.3)

EOT: End of study.

Body measurements - BMI (kg/m^2) by visit- safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 15 months				
N	4	4		8
Mean (SD)	19.3 (2.2)	28.4 (7.0)		23.8 (6.8)
Median	19.4	28.6		21.7
Min ; Max	16.7 ; 21.7	21.6 ; 34.7		16.7 ; 34.7
Change (SD)	3.0 (1.9)	-0.4 (0.6)		1.3 (2.3)
Visit 2, 16 months				
N	3	4		7
Mean (SD)	18.9 (2.3)	28.6 (7.0)		24.4 (7.3)
Median		28.9		22.0
Min ; Max		22.0 ; 34.7		17.1 ; 34.7
Change (SD)	2.2 (1.8)	-0.2 (0.4)		0.8 (1.7)
Visit 2, 17 months				
N	3	3		6
Mean (SD)	19.1 (2.5)	30.8 (6.7)		25.0 (7.8)
Median				22.4
Min ; Max				16.7 ; 34.7
Change (SD)	2.5 (1.7)	-0.2 (0.5)		1.1 (1.8)
Visit 2, 18 months				
N	4	3		7
Mean (SD)	20.2 (2.9)	31.0 (6.8)		24.8 (7.3)
Median	20.7			22.7
Min ; Max	16.7 ; 22.7			16.7 ; 35.2
Change (SD)	2.0 (1.8)	0.0 (0.4)		1.2 (1.7)
Visit 2, 19 months				
N	5	3		8
Mean (SD)	20.0 (2.4)	31.3 (7.1)		24.2 (7.2)
Median	19.8			22.4
Min ; Max	16.9 ; 22.7			16.9 ; 36.0
Change (SD)	1.7 (2.2)	0.3 (0.6)		1.2 (1.9)
Visit 2, 20 months				
N	3	2		5
Mean (SD)	19.9 (3.2)	(7.8)		23.6 (6.8)
Median				23.2
Min ; Max				16.8 ; 34.7
Change (SD)	3.3 (1.2)	0.3 (1.0)		2.1 (1.9)
Visit 2, 21 months				
N	3	2		5
Mean (SD)	20.4 (3.2)	(7.8)		23.9 (6.6)
Median				23.4
Min ; Max				17.0 ; 34.7
Change (SD)	3.7 (1.6)	0.3 (1.0)		2.4 (2.2)
Visit 2, 22 months				
N	3	2		5
Mean (SD)	21.1 (3.6)	(8.5)		24.5 (6.8)
Median				23.7
Min ; Max				17.2 ; 35.7
Change (SD)	4.4 (1.6)	0.8 (0.4)		2.9 (2.3)

EOT: End of study.

Body measurements - BMI (kg/m^2) by visit- safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 23 months				
N	3	1		4
Mean (SD)	20.8 (3.5)	[redacted]		21.9 (3.5)
Median	[redacted]	[redacted]		22.6
Min ; Max	[redacted]	[redacted]		17.3 ; 25.0
Change (SD)	4.1 (1.1)	[redacted]		3.7 (1.3)
Visit 2, 24 months				
N	3	2		5
Mean (SD)	20.9 (3.6)	[redacted] (7.8)		25.0 (7.2)
Median	[redacted]	[redacted]		24.5
Min ; Max	[redacted]	[redacted]		17.4 ; 36.6
Change (SD)	4.3 (1.1)	2.2 (1.1)		3.4 (1.5)
Visit 2, 25 months				
N	5	2		7
Mean (SD)	20.9 (2.5)	[redacted] (7.6)		23.7 (6.0)
Median	22.0	[redacted]		22.6
Min ; Max	18.0 ; 23.4	[redacted]		18.0 ; 36.0
Change (SD)	2.6 (2.9)	1.7 (1.3)		2.4 (2.5)
Visit 2, 26 months				
N	5	2		7
Mean (SD)	21.0 (2.7)	[redacted] (8.1)		23.9 (6.3)
Median	22.2	[redacted]		23.1
Min ; Max	17.9 ; 23.6	[redacted]		17.9 ; 36.7
Change (SD)	2.7 (3.1)	2.1 (0.8)		2.5 (2.6)
Visit 2, 27 months				
N	4	2		6
Mean (SD)	21.9 (2.7)	[redacted] (8.8)		25.2 (6.8)
Median	22.9	[redacted]		23.9
Min ; Max	18.1 ; 23.9	[redacted]		18.1 ; 38.0
Change (SD)	3.8 (3.9)	2.8 (0.1)		3.5 (3.0)
Visit 2, 28 months				
N	4	1		5
Mean (SD)	22.1 (2.7)	[redacted]		22.8 (2.9)
Median	23.1	[redacted]		23.8
Min ; Max	18.2 ; 23.9	[redacted]		18.2 ; 25.9
Change (SD)	3.9 (3.6)	[redacted]		3.8 (3.2)
Visit 2, 29 months				
N	3	2		5
Mean (SD)	22.4 (3.4)	[redacted] (7.1)		25.8 (6.4)
Median	[redacted]	[redacted]		24.9
Min ; Max	[redacted]	[redacted]		18.5 ; 36.0
Change (SD)	5.7 (3.4)	2.0 (1.7)		4.2 (3.3)
Visit 2, 30 months				
N	3	2		5
Mean (SD)	22.0 (3.3)	[redacted] (6.4)		25.5 (6.2)
Median	[redacted]	[redacted]		24.0
Min ; Max	[redacted]	[redacted]		18.2 ; 35.2
Change (SD)	5.4 (2.9)	1.8 (2.5)		3.9 (3.1)

EOT: End of study.

Body measurements - BMI (kg/m^2) by visit- safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 31 months				
N	3	2		5
Mean (SD)	22.3 (2.4)	[redacted] (6.7)		25.8 (6.1)
Median	[redacted]	[redacted]		23.8
Min ; Max				19.5 ; 35.7
Change (SD)	5.6 (2.8)	2.0 (2.1)		4.2 (3.0)
Visit 2, 32 months				
N	3	2		5
Mean (SD)	22.1 (2.1)	[redacted] (6.7)		25.7 (6.1)
Median	[redacted]	[redacted]		23.6
Min ; Max				19.7 ; 35.7
Change (SD)	5.5 (2.7)	2.0 (2.1)		4.1 (2.9)
Visit 2, 33 months				
N	2	2		4
Mean (SD)	[redacted] (3.0)	[redacted] (6.6)		26.2 (6.8)
Median	[redacted]	[redacted]		24.9
Min ; Max				19.4 ; 35.5
Change (SD)	4.3 (2.6)	1.9 (2.3)		3.1 (2.4)
Visit 2, 34 months				
N	2	2		4
Mean (SD)	[redacted] (3.1)	[redacted] (6.7)		26.7 (6.8)
Median	[redacted]	[redacted]		25.5
Min ; Max				20.0 ; 36.0
Change (SD)	5.0 (2.5)	2.3 (2.1)		3.6 (2.4)
Visit 2, 35 months				
N	2	2		4
Mean (SD)	[redacted] (3.0)	[redacted] (7.7)		27.1 (7.4)
Median	[redacted]	[redacted]		25.4
Min ; Max				20.0 ; 37.4
Change (SD)	4.9 (2.5)	3.0 (1.1)		4.0 (1.9)
Visit 2, 36 months				
N	1	2		3
Mean (SD)	[redacted]	[redacted] (7.0)		29.4 (6.9)
Median	[redacted]	[redacted]		[redacted]
Min ; Max				
Change (SD)		3.2 (1.8)		3.0 (1.3)
Visit 2, 37 months				
N	1	1		2
Mean (SD)	[redacted]	[redacted]		[redacted] (2.5)
Median	[redacted]	[redacted]		[redacted]
Min ; Max				
Change (SD)				3.5 (1.4)
Visit 2, 38 months				
N	1	1		2
Mean (SD)	[redacted]	[redacted]		[redacted] (2.5)
Median	[redacted]	[redacted]		[redacted]
Min ; Max				
Change (SD)				3.5 (1.5)

EOT: End of study.

Body measurements - BMI (kg/m^2) by visit- safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 39 months				
N	1	1		2
Mean (SD)	[redacted]	[redacted]		[redacted] (2.9)
Median				
Min ; Max				
Change (SD)				3.2 (1.8)
Visit 2, 40 months				
N	1	1		2
Mean (SD)	[redacted]	[redacted]		[redacted] (2.3)
Median				
Min ; Max				
Change (SD)				3.6 (1.3)
Visit 2, 41 months				
N	1	1		2
Mean (SD)	[redacted]	[redacted]		[redacted] (2.9)
Median				
Min ; Max				
Change (SD)				3.2 (1.8)
Visit 2, 42 months				
N	1	1		2
Mean (SD)	[redacted]	[redacted]		[redacted] (2.1)
Median				
Min ; Max				
Change (SD)				3.8 (1.0)
Visit 2, 43 months				
N	1	1		2
Mean (SD)	[redacted]	[redacted]		[redacted] (2.2)
Median				
Min ; Max				
Change (SD)				3.7 (1.1)
Visit 2, 44 months				
N	1	2		3
Mean (SD)	[redacted]	[redacted] (7.2)		29.8 (6.7)
Median				
Min ; Max				
Change (SD)		3.3 (1.6)		3.4 (1.2)
Visit 2, 45 months				
N	1	2		3
Mean (SD)	[redacted]	[redacted] (7.2)		29.7 (6.8)
Median				
Min ; Max				
Change (SD)		3.3 (1.6)		3.4 (1.2)
Visit 2, 46 months				
N	1	1		2
Mean (SD)	[redacted]	[redacted]		[redacted] (2.4)
Median				
Min ; Max				
Change (SD)				3.6 (1.3)

EOT: End of study.

Body measurements - BMI (kg/m^2) by visit- safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 47 months				
N	1	1		2
Mean (SD)	[redacted]			[redacted] (1.8)
Median				
Min ; Max				
Change (SD)				4.0 (0.7)
Visit 2, 48 months				
N	1	1		2
Mean (SD)	[redacted]			[redacted] (1.6)
Median				
Min ; Max				
Change (SD)				4.1 (0.6)
Visit 2, 49 months				
N	1			1
Mean (SD)	[redacted]			[redacted]
Median				
Min ; Max				
Change (SD)				
Visit 2, 50 months				
N	1			1
Mean (SD)	[redacted]			[redacted]
Median				
Min ; Max				
Change (SD)				
Visit 2, 51 months				
N	1			1
Mean (SD)	[redacted]			[redacted]
Median				
Min ; Max				
Change (SD)				
Visit 2, 52 months				
N	1			1
Mean (SD)	[redacted]			[redacted]
Median				
Min ; Max				
Change (SD)				
Visit 2, 53 months				
N	1			1
Mean (SD)	[redacted]			[redacted]
Median				
Min ; Max				
Change (SD)				
Visit 2, 54 months				
N	1			1
Mean (SD)	[redacted]			[redacted]
Median				
Min ; Max				
Change (SD)				

EOT: End of study.

Body measurements - BMI (kg/m^2) by visit- safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 55 months				
N	1			1
Mean (SD)	[redacted]			[redacted]
Median				
Min ; Max				
Change (SD)				
Visit 2, 56 months				
N	1			1
Mean (SD)	[redacted]			[redacted]
Median				
Min ; Max				
Change (SD)				
Visit 2, 57 months				
N	1			1
Mean (SD)	[redacted]			[redacted]
Median				
Min ; Max				
Change (SD)				
Visit 2, 58 months				
N	1			1
Mean (SD)	[redacted]			[redacted]
Median				
Min ; Max				
Change (SD)				
Visit 2, 60 months				
N	1			1
Mean (SD)	[redacted]			[redacted]
Median				
Min ; Max				
Change (SD)				
Visit 2, 61 months				
N	1			1
Mean (SD)	[redacted]			[redacted]
Median				
Min ; Max				
Change (SD)				
Visit 2, 62 months				
N	1			1
Mean (SD)	[redacted]			[redacted]
Median				
Min ; Max				
Change (SD)				
Visit 2, 63 months				
N	1			1
Mean (SD)	[redacted]			[redacted]
Median				
Min ; Max				
Change (SD)				

EOT: End of study.

Body measurements - BMI (kg/m^2) by visit- safety analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Visit 2, 64 months				
N		1		1
Mean (SD)		[redacted]		
Median				
Min ; Max				
Change (SD)				
Visit 2, 65 months				
N		1		1
Mean (SD)		[redacted]		
Median				
Min ; Max				
Change (SD)				
Visit 2, 66 months				
N		1		1
Mean (SD)		[redacted]		
Median				
Min ; Max				
Change (SD)				
Visit 2, 67 months				
N		1		1
Mean (SD)		[redacted]		
Median				
Min ; Max				
Change (SD)				
Visit 2, 68 months				
N		1		1
Mean (SD)		[redacted]		
Median				
Min ; Max				
Change (SD)				
EOT				
N	9	8	1	18
Mean (SD)	20.9 (2.2)	31.1 (7.3)	[redacted]	26.0 (7.2)
Median	20.5	31.7		23.0
Min ; Max	18.3 ; 24.3	21.4 ; 41.3		18.3 ; 41.3
Change (SD)	4.2 (2.8)	1.6 (1.8)		2.8 (2.7)

EOT: End of study.

14.3.7 Other safety observations listings

14.3.7.1 Vital signs - safety analysis set

Patient ID/ Age(yrs)/ Treatment	Visit	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Pulse (beats/min)
[redacted]				

ND: not done, NA: not applicable

Vital signs - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Visit	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Pulse (beats/min)
[redacted]				

ND: not done, NA: not applicable

Vital signs - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Visit	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Pulse (beats/min)
[redacted]				

ND: not done, NA: not applicable

Vital signs - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Visit	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Pulse (beats/min)
[redacted]				

ND: not done, NA: not applicable

14.3.7.2 Body measurements - safety analysis set

Patient ID/ Age(yrs)/ Treatment	Visit	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]				

BMI: body mass index, ND: not done
Height(cm) is collected at visit 1.

Body measurements - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Visit	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]				

BMI: body mass index, ND: not done
Height(cm) is collected at visit 1.

Body measurements - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Visit	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]				

BMI: body mass index, ND: not done
Height(cm) is collected at visit 1.

Body measurements - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Visit	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]				

BMI: body mass index, ND: not done
Height(cm) is collected at visit 1.

Body measurements - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Visit	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]				

BMI: body mass index, ND: not done
Height(cm) is collected at visit 1.

Body measurements - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Visit	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]				

BMI: body mass index, ND: not done
Height(cm) is collected at visit 1.

Body measurements - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Visit	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]				

BMI: body mass index, ND: not done
Height(cm) is collected at visit 1.

Body measurements - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Visit	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]				

BMI: body mass index, ND: not done
Height(cm) is collected at visit 1.

Body measurements - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Visit	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]				

BMI: body mass index, ND: not done
Height(cm) is collected at visit 1.

Body measurements - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Visit	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]				

BMI: body mass index, ND: not done
Height(cm) is collected at visit 1.

Body measurements - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Visit	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]				

BMI: body mass index, ND: not done
Height(cm) is collected at visit 1.

Body measurements - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Visit	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]				

BMI: body mass index, ND: not done
Height(cm) is collected at visit 1.

Body measurements - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Visit	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]				

BMI: body mass index, ND: not done
Height(cm) is collected at visit 1.

Body measurements - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Visit	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]				

BMI: body mass index, ND: not done
Height(cm) is collected at visit 1.

Body measurements - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Visit	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]				

BMI: body mass index, ND: not done
Height(cm) is collected at visit 1.

Body measurements - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Visit	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]				

BMI: body mass index, ND: not done
Height(cm) is collected at visit 1.

Body measurements - safety analysis set

Continued...

Patient ID/ Age(yrs)/ Treatment	Visit	Height (cm)	Body weight (kg)	BMI (kg/m^2)
[redacted]				

BMI: body mass index, ND: not done
Height(cm) is collected at visit 1.

15 References

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