15 September 2016
EMA/18173/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

NovoThirteen

catridecacog

Procedure no: EMEA/H/C/002284/P46/016

Note

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

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1. Introduction

On 19-04-2016, the MAH submitted a long term safety extension trial (F13CD-3720) where 60 subjects with congenital FXIII A subunit deficiency of which 16 were children and adolescents were administered, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

2. Scientific discussion

2.1. Information on the development program

These data are also submitted as part of the extension safety study of the study F13CD-1725

2.2. Information on the pharmaceutical formulation used in the study

The rFXIII was supplied by the MAH as a sterile lyophilised powder for injection in single use vials of 2500 IU (15 mg) per vial. Each vial was to be reconstituted in 3.2 mL sterile water for injection (SWFI). A single dose of reconstituted rFXIII (35 IU/kg) was administered as an intravenous injection.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

Study F13 CD 3720: A multi-centre, open-label, single-arm, and multiple dosing trial on safety of monthly replacement therapy with recombinant factor XIII (rFXIII) in subjects with congenital factor XIII deficiency.

The trial enrolled 60 subjects with congenital FXIII A subunit deficiency in which 16 are paediatric and adolescents received recombinant FXIII Novothirteen® (Catridecacog) at a monthly dose of 35 UI/Kg body weight.

2.3.2. Clinical study

Clinical study F13CD-3720 "A multi-centre, open-label, single-arm, and multiple dosing trial on safety of monthly replacement therapy with recombinant factor XIII (rFXIII) in subjects with congenital factor XIII deficiency".

Description

The study was a multi-centre, open-label, single-arm, and multiple dosing trial on safety of monthly replacement therapy with recombinant factor XIII (rFXIII) in subjects with congenital factor XIII deficiency. 60 subjects with congenital FXIII A subunit deficiency in which 16 are paediatric and adolescents received recombinant FXIII Novothirteen® (Catridecacog) at a monthly dose of 35 UI/Kg body weight were enrolled. This study was a safety extension study of the study F13CD-1725.

A total of 60 subjects were enrolled and exposed to trial drug (covering 63 subject IDs, which includes 3 subjects who withdrew and re-enrolled in the the trial with new subject IDs):

- 34 subjects enrolled into trial F13CD-3720 from trial F13CD-1725

- 26 new subjects were enrolled

- 44 subjects completed the trial.

Methods

Objective(s)

Primary objective:

- To assess the long term safety of monthly replacement therapy with rFXIII when used for prevention of bleeding episodes and for the treatment of breakthrough bleeding in subjects with congenital FXIII deficiency.

Secondary objectives:

- To evaluate the efficacy of monthly replacement therapy with rFXIII when used for the prevention of bleeding episodes and for the treatment of breakthrough bleeding in subjects with congenital FXIII deficiency.

- To evaluate the steady state pharmacokinetic profile after monthly replacement therapy with rFXIII.

Assessor's comment: Primary and secondary objectives are acceptable.

Study design

This was as a multi-centre, multi-national, open-label, single-arm and multiple dosing, phase 3b trial conducted for the purpose of providing information on the long-term safety and efficacy of rFXIII used to treat subjects with congenital FXIII deficiency. The trial design resembled that of the Novo Nordisk phase 3a trial F13CD-1725.

All subjects who completed Trial F13CD-1725 were offered to be enrolled in the extension trial. Amendment No. 8 allowed enrolment of new subjects directly in the extension trial

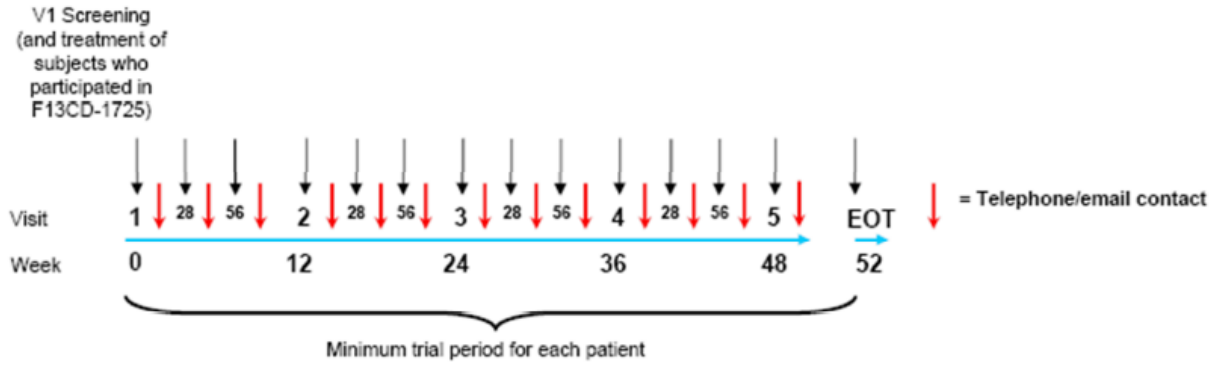
Subjects were asked to participate for a minimum of 52 weeks, consisting of a screening visit to assess subjects' eligibility followed by monthly administrations of rFXIII. For subjects that participated in trial F13CD-1725, visit 1 had to occur on the same day as the end-of-trial visit for trial F13CD-1725.

With the introduction of Amendment No 14 (14-May-2012), each subject was given the option of participating in a PK session once he/she had received a minimum of 5 injections with rFXIII for the purpose of assessing the drug' s steady state PK properties. Subjects who took part in the PK evaluation provided blood samples for the PK assessment prior to dosing and again at 1 and 2 hours, and at 3, 7, 14, and 28 days post-dose.

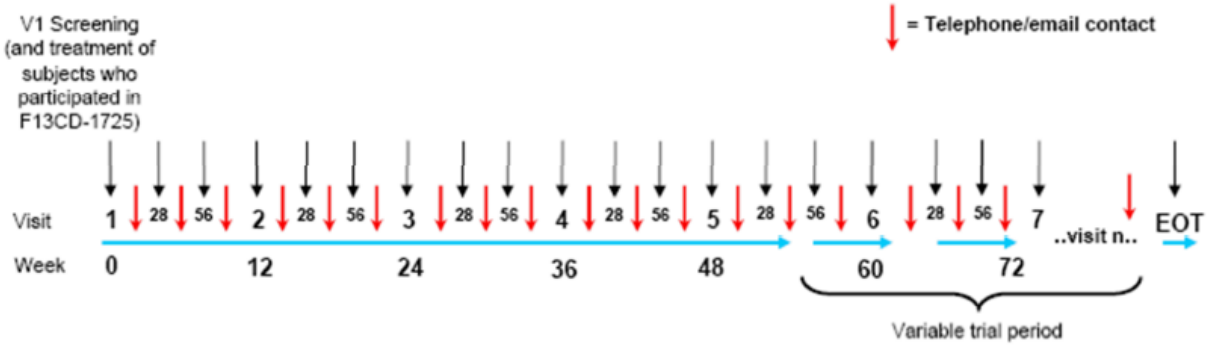
End of the trial:

As per the protocol, the end of the trial was dependent on the launch of rFXIII, and was defined as the LPLV. If the subject had participated in the trial for at least 48 weeks at the time of product launch then the end-of-trial visit was to be completed 28 days (± 2 days) after the next appropriate planned

visit to the clinic.



Alternative 2: Trial Product is not on market in time for subjects visit 5 – continue with the previous visit schedule until market introduction/launch, and then schedule EOT visit 28 +/- 2 days after last assessment visit to the clinic



Study population /Sample size

All enrolled subjects had congenital FXIII A-subunit deficiency (confirmed by genotyping).

Inclusion criteria:

- For subjects who participated in F13CD-1725:

Previous participation (means up to and inclusive visit 16, [End of Trial]) in F13CD-1725

- For all other subjects:

- Diagnosis of congenital FXIII A-subunit deficiency (confirmed by genotyping at screening visit or documented results from previously performed genotyping)

- Body weight at least 20 kg

Exclusion Criteria:

- Known neutralizing antibodies (inhibitors) towards FXIII

- Any known congenital or acquired coagulation disorder other than congenital FXIII deficiency

- Platelet count (thrombocytes) of less than 50 × 10^9/L. For subjects who participated in F13CD-1725 platelet count from visit 15 in F13CD-1725 was to be used for evaluation.

- Known or suspected allergy to trial products or related products

- Renal insufficiency defined as currently requiring dialysis therapy

- Any history of confirmed venous or arterial thrombo-embolic events

- Females of childbearing potential who are pregnant, breastfeeding or are not using adequate contraceptive methods

Treatments

A single dose of reconstituted rFXIII (35 IU/kg) was administered as an intravenous injection.

Outcomes/endpoints

Efficacy endpoints:

- Rate (number per subject year) of bleeding episodes requiring treatment with a FXIII containing product during the rFXIII treatment period subdivided according to spontaneous, traumatic and intracranial bleeding.

- Haemostatic response to rFXIII after a single dose of 35 IU/kg for treatment of breakthrough bleeding episodes. Assessments were based on a 4-point scale as: Excellent, good/effective, moderate/partly effective or poor (no improvement or bleeding the same or worsened, other rFXIII product required).

- Withdrawals due to lack of efficacy of rFXIII treatment.

- Steady-state PK in subjects with congenital FXIII deficiency after monthly replacement therapy with rFXIII. The PK parameters were based on:

  – FXIII activity (assessed by the Berichrom® assay) (all parameters)

  - ELISAs (FXIII A2B2 tetramer) (selected parameters as exploratory/supportive analyses)

Safety endpoints:

- Serious and non-serious adverse events (primary endpoint)

- Antibody and inhibitor development (secondary endpoint)

- Laboratory parameters (haematology, biochemistry, urinalysis, coagulation-related parameters, immunogenicity) (secondary endpoint)

- Vital signs and physical examinations (secondary endpoint)

Statistical Methods

The primary endpoint and secondary safety endpoints were evaluated descriptively.

Listings of adverse events (AEs) and serious adverse events (SAEs) reported during the trial period, including pertinent clinical information, were provided. The study flagged events related to a diagnosis. Any listed AE regarded as a symptom (belonging to a reported diagnosis) was included in the summary tables only when the symptom was classified as serious.

Secondary efficacy endpoints included

1) Rate (number per subject year) of bleeds requiring treatment with a FXIII containing product during the rFXIII treatment period and

2) Number of subjects withdrawn from the trial due to lack of efficacy of rFXIII treatment (as judged by the investigator).

The number of bleeding episodes requiring treatment with a FXIII-containing product was evaluated by a Poisson model (log-link), similar to the model used in trial F13CD-1725 using baseline age as a covariate. The model also took into account those subjects withdrawing before the end-of-trial, by adjusting the length of time under observation. The estimated rate was based on the average baseline age of the subjects in the trial, adjusting for over-dispersion, which was estimated by Pearson's chisquare statistic divided by its degrees of freedom.

The number of subjects withdrawn from the trial due to lack of efficacy of rFXIII treatment was to be tabulated and listed.

The PK endpoints were calculated using non-compartmental methods based on the Berichrom® activity assay. PK profiles were not baseline adjusted prior to PK calculations. All PK parameters derived from FXIII activity were listed individually and summarised by treatment. Profiles of FXIII activity versus time were plotted as individual curves and as mean curves on the original scale and on the logarithmic scale. FXIII activity levels were further listed individually and summarised by treatment and time point.

Results

Recruitment/ Number analysed

The trial enrolled 60 subjects with congenital FXIII A subunit deficiency in which 16 are paediatric and adolescents received recombinant FXIII Novothirteen® (Catridecacog) at a monthly dose of 35 UI/Kg body weight.

Baseline data

The trial population had a mean age of 31.0 years (range 7.0−77.0 years) and most subjects (64%) were male.

The majority (59%) of subjects were White. Weight and height varied considerably as expected for this trial population which included both adults and paediatric subjects. None of the subjects were positive for anti-rFXIII antibodies at baseline. Most subjects had a normal physical examination at baseline and all pregnancy tests for females of childbearing age were negative.

Efficacy results

In this extension trial, there were 60 unique subjects (63 subject IDs) with congenital FXIII deficiency that received trial drug (rFXIII). Monthly administration of rFXIII was effective in preventing bleeds that required treatment with a FXIII containing product in subjects with FXIII A-subunit deficiency.

The geometrical mean terminal half-life was 13.7 days and the geometrical mean trough FXIII activity level after 28 days was 0.158 IU/mL.

The mean trough FXIII activity level at 28 days post-dose (0.173 IU/mL) was almost identical to the pre-dose level (0.188 IU/mL), indicative of a steady state situation.

The annual mean bleeding rate (number of bleeds that required treatment with a FXIII-containing product per subject year) was low: 0.043 bleeds/subject/year.

In 16 subjects below the age of 18 years at enrolment, 5 treatment-requiring bleeds occurred in 4 subjects (mean rate: 0.104 bleeds/subject/year), whereas the corresponding rate in 47 subjects above 18 years was 0.022 bleeds/subject/year, as a result of 3 bleeds in 3 subjects

The estimated mean rate of bleeds treated with a FXIII-containing product was 0.021 bleeds/year during the trial period with a 95% CI [0.0062; 0.073] (at the mean age of 31.0 years).

A total of 53 subjects did not have FXIII treatment-requiring bleeds.

Assessor's comments :

Treatment-requiring bleeds are superior in the 16 subjects below the age of 18. (0.104 bleeds/subjects/year versus 0.022 bleeds/subjects/year in the patients who are superior of 18).

Because of the low number of patients, comparison between ages would have been insignificant.

However, it is asked to the MAH to discuss this point.

Anyway, the main conclusion on efficacy in the current trial is that the observed rates (both the adjusted and the unadjusted) of FXIII-treatment-requiring bleeding episodes were low.

Safety results

Demography of trial population

The trial population had a mean age of 31.0 years (range 7.0−77.0 years) and most subjects (64%) were male. None of the subjects were positive for anti-rFXIII antibodies at baseline. Most subjects had a normal physical examination at baseline and all pregnancy tests for females of childbearing age were negative.

Exposure

A total of 60 unique subjects with congenital FXIII deficiency (63 subject IDs, which includes 3 re-enrolled subjects with new subject IDs) received rFXIII. Of these 60 patients, 16 were children and adolescents, 34 had completed study F13CD-1725 and 26 were newly enrolled patients.

Monthly dose was of 35 IU/kg. The number of exposures was 2,410 in the 60 unique subjects, corresponding to 186.5 subject years. Subjects received between 2 and 69 doses per subject.

Adverse events

A total of 920 TEAEs were reported in 56 (93.3%) subjects; the majority were mild (785 events in 54 subjects) or moderate (119 events in 26 subjects) and the most commonly reported were headache (77 events in 19 subjects) and nasopharyngitis (50 events in 20 subjects). Sixteen (16) AEs in 12 subjects were classified as severe, of which 12 serious events.

Nineteen (19) serious adverse events were observed in 12 subjects and were evaluated as unlikely related to trial drug by the investigator:

Table 12–6 Summary of serious adverse events – full analysis set

	Avecia				Novo Nordisk				Total			
	rFXIII 35 IU/kg				rFXIII 35 IU/kg				rFXIII 35 IU/kg			
	N	(%)	E	[R]	N	(%)	E	[R]	N	(%)	E	[R]
Number of subjects*	26				59				60			
Number of exposures	122				2288				2410			
All adverse events	0	(0.0)	0	[0.0]	12	(20.3)	19	[0.8]	12	(20.0)	19	[0.8]
Congenital, Familial And Genetic Disorders	0	(0.0)	0	[0.0]	1	(1.7)	2	[0.1]	1	(1.7)	2	[0.1]
Atrial septal defect	0	(0.0)	0	[0.0]	1	(1.7)	1	[0.0]	1	(1.7)	1	[0.0]
Patent ductus arteriosus	0	(0.0)	0	[0.0]	1	(1.7)	1	[0.0]	1	(1.7)	1	[0.0]
Gastrointestinal Disorders	0	(0.0)	0	[0.0]	1	(1.7)	1	[0.0]	1	(1.7)	1	[0.0]
Inguinal hernia	0	(0.0)	0	[0.0]	1	(1.7)	1	[0.0]	1	(1.7)	1	[0.0]
Infections And Infestations	0	(0.0)	0	[0.0]	2	(3.4)	2	[0.1]	2	(3.3)	2	[0.1]
Diverticulitis	0	(0.0)	0	[0.0]	1	(1.7)	1	[0.0]	1	(1.7)	1	[0.0]
Otitis media chronic	0	(0.0)	0	[0.0]	1	(1.7)	1	[0.0]	1	(1.7)	1	[0.0]
Injury, Poisoning And Procedural Complications	0	(0.0)	0	[0.0]	5	(8.5)	10	[0.4]	5	(8.3)	10	[0.4]
Chest injury	0	(0.0)	0	[0.0]	1	(1.7)	1	[0.0]	1	(1.7)	1	[0.0]
Fall	0	(0.0)	0	[0.0]	2	(3.4)	2	[0.1]	2	(3.3)	2	[0.1]
Head injury	0	(0.0)	0	[0.0]	2	(3.4)	2	[0.1]	2	(3.3)	2	[0.1]
Laceration	0	(0.0)	0	[0.0]	1	(1.7)	1	[0.0]	1	(1.7)	1	[0.0]
Multiple fractures	0	(0.0)	0	[0.0]	1	(1.7)	1	[0.0]	1	(1.7)	1	[0.0]
Road traffic accident	0	(0.0)	0	[0.0]	2	(3.4)	2	[0.1]	2	(3.3)	2	[0.1]
Spinal cord injury	0	(0.0)	0	[0.0]	1	(1.7)	1	[0.0]	1	(1.7)	1	[0.0]
Nervous System Disorders	0	(0.0)	0	[0.0]	2	(3.4)	2	[0.1]	2	(3.3)	2	[0.1]
Cerebral ischaemia	0	(0.0)	0	[0.0]	1	(1.7)	1	[0.0]	1	(1.7)	1	[0.0]
Headache	0	(0.0)	0	[0.0]	1	(1.7)	1	[0.0]	1	(1.7)	1	[0.0]
Pregnancy, Puerperium And Perinatal Conditions	0	(0.0)	0	[0.0]	1	(1.7)	1	[0.0]	1	(1.7)	1	[0.0]
Ectopic pregnancy	0	(0.0)	0	[0.0]	1	(1.7)	1	[0.0]	1	(1.7)	1	[0.0]
Psychiatric Disorders	0	(0.0)	0	[0.0]	1	(1.7)	1	[0.0]	1	(1.7)	1	[0.0]
Suicide attempt	0	(0.0)	0	[0.0]	1	(1.7)	1	[0.0]	1	(1.7)	1	[0.0]

N: Number of subjects with adverse event. %: Proportion of subjects with adverse event
E: Number of adverse events
R: Number of adverse events per 100 exposures (E/Number of exposures*100)
Non-serious adverse events that are symptoms of other adverse events are not included.
* : When summarising AEs, 3 subjects re-enrolled in the trial (18301, 20112 and 31302) are assigned their initial subject IDs (18101, 20103 and 31301) to avoid double-counting.

The atrial septal defect and the ductus arteriosus were associated with the newborn of a subject rather than the subject herself.

The SAEs in paediatric patients were:

- A headache in a 8 year old (moderate), a second SAE of head injury (severe) occurred in the same subject (banging head from a fall) 5 months later.

- A 12 year-old subject sustained a severe laceration to his forehead.

- One female subject attempted suicide at age 14 years, approximately 4 years after starting treatment with rFXIII.

Assessor's comment:

No concern related to SAEs in the study population or in the paediatric patients are seen from these data.

Investigators evaluated 8 AEs in 7 subjects as possibly or probably related to the trial product including:

-Four (4) events in 3 subjects evaluated as probably related to rFXIII by the investigator included 2 events of dosing error (1 event of wrong dose in a 15-year-old male subject and one non-severe event of overdose in an 8-year-old male subject), an event of arthralgia/knee pain in the same 8-year-old subject starting 22 days since his latest dose and one event of leukopenia in a 15-year-old female subject starting 28 days since the previous rFXIII dose and lasting 115 days.

Assessor's comment:

Half of the related events occurred in paediatric patients (who represent 27% of the entire study population).

-Two (2) events assessed by the investigator as possibly related to rFXIII including blood detected in stool in a 25-year-old female subject 20 days following her latest rFXIII dose and a non-severe limb injury (bleeding under the toe nail) in a 22-year-old male subject 28 days since the previous rFXIII dose. The event of 'blood in stool', considered as possibly related to product, was categorized as a non-serious symptom.

-Two (2) additional 'possibly related' events were ALAT increased in a 26-year-old male subject 28 days after his previous rFXIII dose and ALP increased in a 63-year-old male subject 28 days since the previous rFXIII dosing. The younger man had increased ALAT on a few occasions, but most of his ALAT results were normal. The older man had alternative aetiologies for the increased ALP including chronic hepatitis C and a liver cyst.

No thromboembolic events, fatal adverse events, anaphylactic or allergic reactions to rFXIII or adverse events leading to withdrawal were reported. No subjects were withdrawn due to lack of efficacy of rFXIII treatment.

44 subjects completed the F13CD-3720 trial. Of the 19 subjects withdrawn from the trial (including the 3 subjects who withdrew and re-enrolled), 3 subjects became pregnant (of which one re-enrolled) and 1 patient wanted to go on commercially available plasma derived FXIII. None of the subjects withdrew due to an AE.

Twelve medication errors classified as MESIs occurred in 8 subjects, and included 10 events of incorrect dose administered, 1 event of wrong reconstitution technique (actual dose ~33.1 IU/kg) and 1 event of overdose (actual dose 80.03 IU/kg or 2.3 times the planned dose and was evaluated by the investigator as mild and probably related to trial product). Medication errors recorded as 'incorrect dose' were close to the approved dose of 35 IU/kg, ranging from 28.2 IU/kg to approximately 37.6 IU/kg. As such they were not reported as an under- or overdose.

Assessor's comment:

Medication errors in paediatric patients (42% of the medication error cases) were 1 incorrect dose administered in a 15 year old patient (mild, probably related), 2 wrong doses administered in a 7 year old patient, 1 overdose (probably related, mild) and 1 incorrect dose administered in a 8 year old. No special trend of medication error is detected.

Through protocol amendment n°6, the investigational product was switched from $rFXIII_{Avecia}$ (3 batches used, 26 subjects received 122 doses) to $rFXIII_{NN}$ (4 batches used in 61 subjects who received 2288 doses). The majority of subjects were exposed to $rFXIII_{NN}$. The rates of AEs were similar for the two

rFXIII drug substances when adjusted for exposure ($rFXIII_{NN}$: 871 events in 56 subjects or 38.1 events per 100 exposures; $rFXIII_{Avecia}$: 49 events in 15 subjects or 40.2 events per 100 exposures).

A total of 306 AEs were reported in 24 rFXIII-naïve subjects not previously participating in trial F13CD-1725, corresponding to 39.9 events per 100 exposures. The AE profile for the treatment-naïve population resembled that of the entire trial.

Assessor's general comment:

The MAH did not provide a specific focus on paediatric population, the MAH is requested to provide a comparison of safety data in paediatric an adult patients as regard to TEAEs, TEAEs assessed as at least possibly related to rFXIII and serious AEs.

Clinical laboratory evaluations

No anti-rFXIII antibodies were detected.

Results on safety laboratory parameters and other safety-related examinations did not indicate clinically relevant changes as a result of rFXIII administration. Laboratory values remained within reference ranges for the majority of measurements. Overall, there were no clinically meaningful changes in haematology, biochemistry, urinalysis, or coagulation related parameters over time.

Haematology: 9 results registered as adverse events but none was related to rFXIII except one leukopenia in a paediatric patient and all were mild except one severe haemorrhagic anaemia resulting from a road traffic accident.

Assessor's comment:

Three of these events occurred in paediatric patients: 1 neutropenia in a 8 year old, 1 leukopenia in a 15 years old (probably related) and 1 haemoglobin decreased in a 11 year old. No concern rises from these data.

Biochemistry: 3 results were recorded as adverse events all were mild but 2 (increased ALAT and increased ALP in 2 adult patients) were assessed as possibly related to rFXIII by the investigators.

Urinalysis: 8 adverse events were recorded and all were mild and assessed as unlikely related to rFXIII by the investigator.

Assessor's comment:

One of the urinalysis events was reported for a 8 years old subject.

Coagulation parameters: 4 events were recorded and evaluated as unlikely related to rFXIII. In addition, an adult patient had an extreme thrombin time value which was not reported as an AE.

Assessor's comment:

One adolescent patient (17 years old) reported a prolonged PT and INR increased and one paediatric patient (7 years old) reported a prolonged aPTT.

Vital signs:

Mean pulse and mean blood pressure readings remained constant over time and within normal range for the population studied. Of note, 3 younger subjects had a low systolic blood pressure reading at multiple visits.

Vital sign readings varied between subjects as expected given the wide range of ages represented in this trial.

Assessor's comment:

Three paediatric patients of 8, 10 and 7 years old had systolic blood pressures between 75 and 99 mmHg, no concern is raised.

Physical examination

Overall there were no trends in abnormal physical findings that concerned several subjects within the body systems evaluated; however there were a few clinically relevant findings that were clinically significant including:

- bruising on the knee cap of a 10-year-old subject

- a haematoma in the right forearm of a 16-year-old subject

- a scalp wound at week 24 in a 27-year-old

- a bruised palm in a 43-year-old subject

- a treatment-requiring bleed (from the nostrils) reported in an 8-year-old subject, 19 days post dose, after week 132

Clinically relevant (but not clinically significant) abnormal findings reported during the trial included:

- a haematoma on one knee in a 52-year-old subject at week 84, and a wound on the left finger of the same subject at week 24 that was reported as an AE

- a haematoma on the right hip in a 77-year-old subject (week 24) reported as a non-treatment emergent AE

- a cut on the right hand in a 15-year-old subject at week 24 and contusion on the thumb of the same subject reported as an AE at the end-of-trial visit

- a haematoma on the lower right tibia in a 7-year-old subject at week 48

- bruising on the left hip in an 8-year-old subject at week 24

- cuts on the face of 2 young adults at week 24 (lip laceration reported as an AE)

- bruising on one shin and superficial laceration to the index finger noted for an 8-year-old subject at weeks 36 and 84, respectively

- mild, generalized joint pain reported as an AE (unlikely related, not recovered) in a 22-year-old subject at the end-of-trial visit.

Assessor's comment:

No trend of physical abnormal observations rises from these data, 7 of these findings were observed in paediatric patients but no safety concern emerges.

Pregnancy cases

Five (5) cases of pregnancy arose during the trial:

- One subject experienced a "spontaneous" miscarriage at less than 22 weeks gestation. She received her last dose of rFXIII 2 weeks prior to losing the pregnancy. She had previously been pregnant 5 times and had given birth to 3 healthy children. She was withdrawn from the study after being treated with rFXIII for 4.5 years.

- A second subject had a positive pregnancy test at approximately 4 weeks gestation. She received her last dose of trial product 27 days before this test result and was withdrawn from the trial the day after. Eight months later the subject gave birth to a full-term, healthy infant. No complications were reported during the normal pregnancy. The newborn had a small atrial septal defect (ongoing) and a small patent ductus arteriosus which has recovered. In both these cases the cause of events was assessed as unlikely related to trial product by the investigator. The fetus was exposed to trial product during the first trimester of pregnancy.

- The third case concerned a 27-year old subject who became pregnant after being treated with rFXIII for 1 month. She had previously given birth to 2 healthy infants and was not interested in having more children. Therefore, the pregnancy was terminated. The subject was withdrawn from the study. She later re-enrolled with another ID.

- The fourth case: The same subject re-enrolled in the trial with another subject ID. She had a positive pregnancy test at 32 years of age after being on the trial the second time for approximately 4 years. Gestational age at the time of reporting was 3 weeks. She completed her end-of-trial visit at the next scheduled visit. She had had 3 previous pregnancies, and had given birth to 2 healthy children at the time of reporting. She later gave birth to a full-term, healthy infant. After the delivery the subject developed a postpartum haemorrhage due to uterine atony.

- The fifth case concerned a 30 year old subject who had a positive home pregnancy test after receiving rFXIII for approximately 4 years. Trial product was discontinued when the pregnancy was discovered. Gestational age at the time of reporting was 5 weeks 3 days. A routine ultrasound at gestational week 7 showed that the pregnancy was ectopic. The pregnancy was terminated as a result.

2.3.3. Discussion on clinical aspects

Safety:

For the 60 unique subjects with congenital FXIII deficiency who received a cumulative amount of 2410 administrations, 920 TEAEs were reported (in 56 subjects) and no particular safety concerns were identified. No thromboembolic events, anaphylactic/allergic events, fatal adverse events or adverse events leading to withdrawal were reported. Serious adverse events were few (19 events in 12 subjects) and evaluated as unlikely related to trial drug.

However 12 medication errors classified as MESIs occurred in 8 subjects, including 1 overdose. Five of the 12 medication error cases occurred in paediatric patients, but no specific trend of medication error has been detected.

Results on safety laboratory parameters and other safety-related examinations did not indicate clinically relevant changes.

No new significant information was received, no change of SmPC is thus required.

However, the MAH did not provide a specific focus on paediatric population, the MAH should therefore provide a comparison of safety data in paediatric an adult patients as regard to TEAEs, TEAEs assessed as at least possibly related to rFXIII and serious AEs.

Efficacy:

Main efficacy parameters are in concordance with the pivotal F13CD-1725 study and highlight the long term efficacy of once-montlhy rFXIII in adult and paediatric subjects.

Indeed, unadjusted (with regard to age) mean annualised bleeding rates (ABR) was low (0.043 bleeds/subjects/year).

However, the MAH is asked to discuss the differences between treatment requiring bleeds on paediatric population and non-paediatric population.

3. Rapporteur's CHMP overall conclusion and recommendation

☒ **Fulfilled:**

☐ **Not fulfilled:**

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1- The MAH should explain the differences between treatments requiring bleeds on paediatric population and non-paediatric population.

2- An information in the section 5.1 on the SmPC on first results in paediatric population would have been interesting. The MAH is asked to discuss this point and to propose a wording.

3- The MAH should provide a comparison of safety data in paediatric an adult patients as regard to TEAEs, TEAEs assessed as at least possibly related to rFXIII and serious AEs.

4- Information on exposed patients and paediatric population should be updated in section 4.8 of the SmPC through a type II variation.

MAH responses to Request for supplementary information

Response to question 1

In the F13CD-3720 trial, there were a total of 2,410 exposures to rFXIII, and the total observation period amounted to 186.5 subject years. During this period, 7 subjects experienced 8 bleeds that required treatment with a FXIII-containing product making the overall bleeding rate 0.043 bleedings per patient per year. The traumatic bleeding rate was 0.032 (n=6) and the spontaneous bleeding rate was 0.011 (n=2).

As traumatic bleeding episodes are normal events also for people who do not have bleeding disorders, the spontaneous bleeding rate is the most interesting in this context. A spontaneous bleeding rate of 0.011 is equivalent to a FXIII congenital factor A-subunit deficiency patient experiencing one spontaneous bleed every 91 years. Thus, spontaneous bleeds among patients on prophylaxis with 35

IU/kg rFXIII per month is a very rare event. In these data, the two spontaneous bleeds were experienced by a female child of 8 years of age and an adult male of 25 years of age, respectively, and thus no difference between spontaneous treatment requiring bleeds in the paediatric population and non-paediatric population were detected in the F13CD-3720 trial. When looking at all the bleedings that occurred in the trial (n=8), the bleeding rate in patients 6-17 years of age (n=16) was 0.104, and the bleeding rate in patients ≥18 years of age (n=44) was 0.022.

The age-adjusted estimated mean rate of bleeds treated with a FXIII-containing product was 0.021 bleeds/year during the trial period, estimated at the mean age of 31.0 years, with a 95% confidence interval of [0.0062; 0.0734]. Thus the bleeding rate was higher in the lower age group, and younger patients tended to bleed more, driven by traumas.

These results from the F13CD-3720 trial should be seen in the context of the paediatric F13CD- 3835 trial where 6 children below 6 years of age with FXIII congenital factor A-subunit deficiency were followed for a total of 17 patient years and received a total of 214 doses of rFXIII 35 IU/kg. In this trial the annual bleeding rate was zero, thus these very small children did not experience any treatment requiring bleedings at all, neither traumatic nor spontaneous.

The F13CD-3835 CTR was submitted as a PAM in September 2015 via sequence 0050 and assessed "fullfilled" 01-Apr-2016.

Assessor's comment:

Spontaneous bleeding rates in paediatric population and non-paediatric population are similar. The difference between treatment requiring bleeds in paediatric population and non-paediatric population is driven by traumatic bleed rate. Thus is expected to be higher in paediatric population. However, bleeding rates in both population remain low.

Point resolved

Response to question 2

NovoNordisk will submit a general update of the SmPC through a type II variation no later than November 2016 to capture the finalisation of the clinical development programme. Section 5.1 of the updated SmPC will be updated to reflect the total number of exposed paediatric patients and no longer refer to "on-going trials".

Assessor's comment:

The MAH will submit an update of the SmPC with both information requested in questions 2 and 4

Point resolved

Response to question 3

Data to support the response to question 3 are enclosed in Appendix 1.

A total of 920 TEAEs have been reported; 413 TEAEs in 14 children and 507 in 42 adults. The reporting rate is higher in children than in adults, especially within the SOCs Gastrointestinal Disorders (5.8 vs. 1.8%), Injury, Poisoning And Procedural Complications (12.0 vs. 4.3%), Musculoskeletal and Connective Tissue Disorders (9.8% vs. 3.2%), Respiratory, Thoraic and Mediastinal Disorders (11.6 vs. 1.8%). However, the PTs reported more often in children than in adults are events (e.g cough, contusion, ligament sprain, limb injury, arthralgia, pain in extremity, headache and oropharyngeal

pain) which could be expected to occur more often in children than in adults, as children suffer more from infections and minor trauma than adults.

Of these 920 TEAEs 19 were SAEs reported in 12 subjects; 14 SAEs in 9 adults (>18 years) and 5 SAEs in 3 children (<18 years) were evaluated as unlikely to be related to trial drug. A total of 8 AEs in 7 subjects including 4 AEs (possible blood in stool, bleed under toenail, elevation of alanine aminotransferase and elevation of alkaline phosphatase) in 4 adults and 4 AEs (accidental wrong dose, asymptomatic leukopenia, overdose and left knee pain) in 3 children were evaluated as possibly/probably related to the trial drug; all AEs were mild in severity and all subjects were recovered.

In conclusion, children have a higher rate of adverse events than adults, as could be expected from the general morbidity pattern experienced for children with more infections and minor trauma than adults.

Assessor's comment:

As requested, the MAH provided a comparison of safety data in paediatric and non-paediatric population. Concerning TEAEs, the reporting rate was higher in children than those in adults but events reported are expected to occur more often in children than in adults. Concerning SAEs, the reported rates were similar.

Point resolved

Response to question 4

NovoNordisk will submit a general update of the SmPC through a type II variation no later than November 2016 to capture the finalisation of the clinical development programme. Section 4.8 of the updated SmPC will be updated to reflect the total number of exposed patients/ paediatric patients.

Assessor's comment:

The MAH will submit an update of the SmPC with both information requested in questions 2 and 4

Point resolved