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EMA/226659/2016
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/P46/014

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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1. Introduction

On 16 September 2015, the MAH submitted a completed paediatric study for Novothirteen (F13CD-3835), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study F13CD3835 is a stand-alone study.

These data are also submitted as part of the safety extension study of the phase 3b study F13CD-3760.

The MAH stated that F13CD 3835 is not part of the agreed PIP for Novothirteen.

2.2. Information on the pharmaceutical formulation used in the study

The MAH states that the formulation of the study drug administered was identical to that licensed for commercial use.

The trial product is rFXIII. The manufacturing process involves the expression of FXIII as a soluble protein in *Saccharomyces cerevisiae* using recombinant DNA technology. The purified protein is supplied as inactive FXIII [A2] homodimer, identical to endogenous human FXIII. The product is supplied as a sterile, lyophilized powder for i.v. injection, available in single use vials of 2505 IU (15 mg) per vial. The trial product was reconstituted with sterile water (3.2 mL sterile water per vial) and then further diluted with saline (6.0 mL 0.9% w/v sodium chloride). The final concentration was 300 IU/mL.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

- Clinical study F13CD-3835 " A Multi-Centre, Multinational, Open-Label, Single-Arm and Multiple Dosing Trial on Safety and Efficacy of Monthly Replacement Therapy with Recombinant Factor XIII (rFXIII) in Paediatric Subjects with Congenital Factor XIII A-subunit Deficiency".

The trial enrolled paediatric subjects between the age of 1 and 6 years with congenital F XIII A subunit-deficiency witch have completed the PK study F13CD-3760.

2.3.2. Clinical study

Clinical study F13CD-3835 "A Multi-Centre, Multinational, Open-Label, Single-Arm and Multiple Dosing Trial on Safety and Efficacy of Monthly Replacement Therapy with Recombinant Factor XIII (rFXIII) in Paediatric Subjects with Congenital Factor XIII A-subunit Deficiency".

Description

The study was a multinational, open label, single arm and multiple dosing trial designed to provide information on the long term safety and efficacy profile of 35UI/Kg rFXIII every 28 days in paediatric subjects between the age of 1 and 6 years old, with congenital FXIII A-subunit deficiency. The trial enrolled subjects who had completed the pharmacokinetic trial F13CD-3760.

Methods

Objective(s)

Primary objectives: To evaluate the long term safety of monthly replacement with rFXIII when used for prevention of bleeding episodes in paediatric subjects with congenital FXIIIA-subunit deficiency.

Secondary objectives: To investigate the efficacy of monthly replacement therapy with rFXIII when used for prevention of bleeding episodes in paediatric subjects with congenital FXIIIa-subunit deficiency.

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

Study design

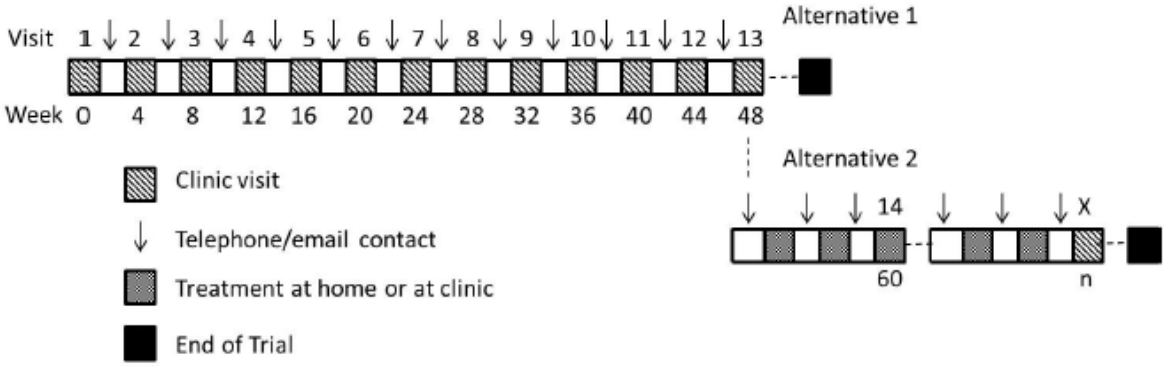
The trial was performed as a multi-centre, multi-national, open label, single arm and multiple dosing phase 3b trial to provide information on the long term safety and efficacy profile of rFXIII in paediatric subjects between the age of 1 and 6 years, with congenital FXIIIA-subunit-deficiency.

The trial enrolled subjects with diagnosis of congenital FXIII A-subunit deficiency who had completed the pharmacokinetic trial F13CD-3760. The trial started with a combined screening, dosing and assessment visit (visit 1). Visit 1 occurred on the same day as the end of trial visit in the F13CD-3760 trial. During the trial period, the subject received rFXIII every four weeks

(28 ± 2 days) either at the clinic during the first year or as home treatment after one year, and only if allowed according to local regulations.

The treatment interval was reduced to less than every four weeks, if deemed necessary by the investigator and sponsor, in case any spontaneous treatment-requiring bleed occurred and if relevant laboratory parameters supported this.

The minimum trial participation was 52 weeks for each subject. Beyond 52 weeks, subjects could continue in the trial until rFXIII became commercially available in their respective country (for use in children between the ages of 1 and 6 years old) up to a maximum of approximately 3.5 years if rFXIII was unavailable. That means the planned length of trial participation for each subject was variable, but was between 1 and approximately 3.5 years



Study population /Sample size

Paediatric subjects between the age of 1 and 6 years with congenital F XIII A subunit-deficiency witch have completed the PK study F13CD-3760. The planned number of subjects was 6. All 6 subjects who were screened were exposed to the trial drug and analysed as part of Full Analysis Set (FAS) and Safety Analysis Set (SAS).

The inclusion criteria for this trial were:

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

Previous participation (means up to and including end of trial visit) in F13CD-3760

The exclusion criteria:

Known or suspected hypersensitivity to trial product or related products

Known history of development of inhibitors against FXIII

Hereditary or acquired coagulation disorder other than FXIII congenital deficiency

Platelet count (thrombocytes) < $50*10^9$/L

Previous history of autoimmune disorder involving autoantibodies e.g., systemic lupus erythematosus

Previous history of arterial or venous thromboembolic events e.g., cerebrovascular accident or deep vein thrombosis

The receipt of any investigational product, except rFXIII, within 30 days of trial enrolment

For US Only: The receipt of any investigational product, except rFXIII or plasma-derived

FXIII, within 30 days of trial enrolment

Non-compliant subject judged by the investigator

Any concomitant serious chronic or acute illness or infection expected to impact compliance or safety, judged by the investigator

Previous participation in this trial. Participation is defined as screened and withdrawn.

Medical, social, or psychosocial factors expected to impact compliance or safety

Any disease or condition which, judged by the investigator, could imply a potential hazard to the subject, interfere with the trial participation or trial outcome including renal and/or liver dysfunction

Inclusion and exclusion criteria are acceptable.

Treatments

The reconstituted trial product was administered as a slow intravenous injection of 35 UI/Kg rFXIII as a rate not to exceed 1-2ml/min). This dose was administered as preventive treatment of bleeding episodes and identical to the dose administered in F13CD-3760. The administration of rFXIII started at the clinic at visit 1. The dosing schedule was every fourth week.

Outcomes/endpoints

Criteria for evaluation-safety

- Primary safety endpoints: Treatment-emergent adverse events.
- Secondary safety endpoints: Antibody and inhibitor development, clinical laboratory parameters, physical examination and vital signs

Criteria for evaluation efficacy

- Rate (number per subject year) of bleeding episodes requiring treatment with a FXIII containing
- Withdrawals due to lack of efficacy of RFXIII treatment.

Assessor comments: Primary and secondary endpoints are considered correct.

Statistical Methods

Primary endpoints analyses:

The AEs and SAEs reported during the trial period were summarized by frequency of events and frequency of subjects with any event. Similar summaries cross-classified by severity and by causal relation to trial product were also made. Furthermore, listings were provided displaying all AEs and SAEs reported during the trial period including pertinent clinical information.

Secondary efficacy endpoints analyses:

The planned analysis included evaluation of the number of bleeding episodes requiring treatment by a Poisson model (log-link) where age at baseline was a covariate and the log individual observation time during the treatment period was used as an offset. Therefore, the length of time under observation for a subject who withdrew before the end of the trial was also taken into account in this model. Over-dispersion was to be estimated by Pearson's chi-square statistic divided by its degrees of freedom.

The rate (number per subject year) of spontaneous, traumatic and intracranial "bleeding episodes requiring treatment" with FXIII-containing products during the rFXIII treatment period was tabulated and listed. The number of bleeding episodes and number of subjects withdrawn from the trial due to lack of efficacy of rFXIII treatment were tabulated and listed.

Results

Recruitment / Number analysed

6 subjects were included.

5 patients between 2-11 years

1 children toddler between 28 days and 23 months.

The study was a multinational, open label, single arm and multiple dosing trial designed to provide information on the long term safety and efficacy profile of 35UI/Kg rFXIII every 28 days in paediatric subjects between the age of 1 and 6 years old, with congenital FXIII A-subunit deficiency.

Baseline data

The mean age of the subjects was 3.0 years (range: 1 to 4 years). Five subjects were children (2–11 years) and 1 was an infant/toddler (28 days–23 months) according to EudraCT age grouping. Half of the subjects were female. Subjects were from the UK (N=3), the US (2), and IS (1). Three (3) subjects were Asian, 2 were White, and 1 was Black/African

American. The mean weight (SD) of subjects was 16.6 kg (3.5) and the mean height (SD) was 98.9 cm (8.3). The mean BMI (SD) of subjects was 16.8 kg/m2 (1.7) and the range was 15kg/m2 to 19 kg/m2. The baseline demographics and other characteristics are shown in the table below:

	rFXIII 35 IU/kg
Number of patients	6
Age at baseline (years)	
N	6
Mean (SD)	3.0 (1.3)
Median	3.5
Min ; Max	1 ; 4
Body mass index (kg/M^2)	
N	6
Mean (SD)	16.8 (1.7)
Median	16.4
Min ; Max	15 ; 19
Body weight (kg)	
N	6
Mean (SD)	16.6 (3.5)
Median	15.4
Min ; Max	14 ; 23
Height (cm)	
N	6
Mean (SD)	98.9 (8.3)
Median	98.4
Min ; Max	89 ; 113

SD: Standard deviation
The body mass index is based on the screening visit only

Efficacy results

At the end of this single-arm safety extension trial in which 6 subjects between the ages of 1 and 6 years old with congenital FXIII A-subunit deficiency received 35 IU/kg rFXIII every 28 days for up to 3.5 years, the following efficacy findings were concluded:

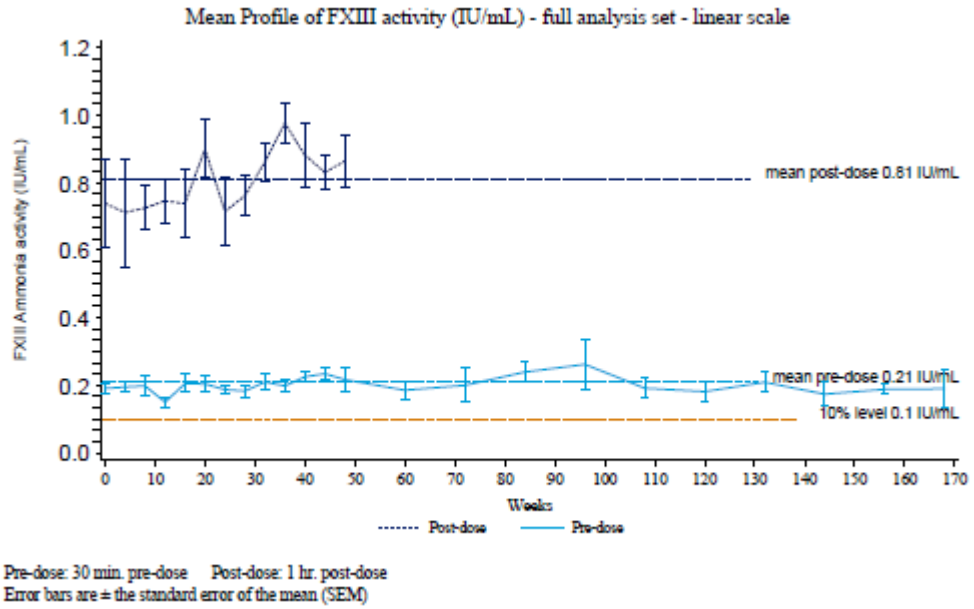
There were no bleeding episodes requiring treatment with a haemostatic agent during the trial.

No subjects withdrew from the trial due to lack of rFXIII treatment efficacy.

There were 14 non-treatment-requiring bleeding episodes in 5 subjects.

As additional information, mean profile of rFXIII activity (IU/ml) are provided (shown in the table below)

FXIII activity levels were evaluated 30 minutes pre-dosing and one hour post-dosing.



Pre-dose: 30 min. pre-dose Post-dose: 1 hr. post-dose
Error bars are ± the standard error of the mean (SEM)

Assessor's comments:
Efficacy results are satisfactory.
However, It seems that appendix 16.2.is missing. Indeed, it is important to know the circumstances per subjects of the 14 non treatment requiring bleeding episodes (spontaneous or induced by trauma, bleeding localization, intensity, etc…).
Therefore, the company should provide the data detailed per subject.

Safety results

At the end of this single-arm safety extension trial in which 6 subjects between the ages of 1 and 6 years old with congenital FXIII A-subunit deficiency received 35 IU/kg rFXIII every 28 days for up to 3.5 years, the following safety findings were concluded:

<u>rFXIII Dosing</u>

All 6 subjects were exposed to rFXIII, with a sum of 214 doses of rFXIII 35 IU/kg over a sum of 198.9 months (mean doses: 35.7(8.6)). The overall mean rFXIII dose (SD) consumed was 35.1 IU/kg (0.2), with a range of 34.9–35.4 IU/kg.

Adverse events

All AEs in the trial were treatment-emergent. There were 100 AEs in the 6 patients, 93 were mild, 7 were moderate and none were severe.

The most frequently reported AEs were upper respiratory tract infection (7 events in 3 subjects), fall (7 events in 3 subjects), rhinorrhoea (7 events in 2 subjects), and pyrexia (6 events in 4 subjects). Two AEs (lymphopenia and gastroenteritis) in 2 subjects were assessed as probably or possibly related to rFXIII by the investigator.

Two SAEs were reported in 1 subject and concerned 2 head injuries caused by falls during play. Neither event was assessed as related to rFXIII by the investigator.

There were 6 MESIs reported in 4 subjects. Of these, 1 was administration of an incorrect dose, 2 were infusion site extravasation (with a temporary drug withdrawal for 1 of the 2 patients), 3 rashes were reported by the same subject on different occasions. All MESIs were assessed as unrelated to rFXIII by the investigator and all subjects recovered from these events.

No thromboembolic events, allergic reactions, or deaths occurred in the trial. None of the AEs in the trial led to withdrawal.

Assessor's comment:

The MAH should provide the case report for the patient who experienced a gastroenteritis and explain the causality assessment.

Concerning one patient, the investigator assessed all 3 rashes as unlikely related to NovoThirteen, however due to temporal relationship the sponsor assessed the third event rash as possible since it happened in the evening of the dosing day. The 2 previous rashes happened nearly 1 month after dosing. IgG and IgE laboratory testings were not performed. However, the patient had rash history and a viral cause seems more plausible. The same patient also experienced an infusion site extravasation, the investigator assessed the event as unlikely related.

One patient experienced extravasation at NovoThirteen infusion that was assessed as unlikely related by the investigator. Infusion was stopped (leaving 0.4 ml) and the extravasation recovered. NovoThirteen was withdrawn temporarily.

Clinical laboratory evaluations

No antibodies against rFXIII were detected in any subjects during the trial.

There were no clinically significant abnormalities as assessed by the investigator regarding haematology, biochemistry, coagulation parameters, or clot solubility laboratory evaluations.

The majority of the physical examination findings were not assessed as clinically significant by the investigator and did not raise any safety concerns.

As for vital signs, the mean pulse (mean [SD]) was slightly higher than the reference range at baseline (113.2 beats per minute [10.6]) but decreased to within the normal range by the end of the trial (94.0 beats per minute [16.8]). There were no apparent changes in mean systolic or diastolic blood pressure during the trial.

2.3.3. Discussion on clinical aspects

Conclusion on efficacy

It should be highlighted that efficacy results do not provide new information and are in concordance with those of the pivotal study (F13CD-3760).

However, the number of subjects is very limited and do not permit to have meaningful conclusions.

To complete the data, the applicant should provide the circumstances of non-treatment requiring bleeding episodes per subjects. (Appendix 16.2.6).

Safety

No new safety data rise from these study results that would change the safety profile. Once-monthly rFXIII was well tolerated in 6 paediatric subjects treated from 1.8 to 3.5 years for a total of 16.6 subject years. There were no thromboembolic events, possibly or probably related allergic reactions or antibodies against rFXIII. Two adverse events of lymphopenia and gastroenteritis were assessed as possibly or probably related to NovoThirteen. However, one patient experienced 3 rashes of which 1 was initially considered as possible by the sponsor only, but a viral etiology seemed more likely.

None of the AEs in the trial led to withdrawal but one drug temporary withdrawal was necessary for one patient who experienced extravasation at infusion.

No new safety information is deemed necessary for implementation in the PI.

The MAH should however provide complementary information as requested.

3. Additional clarification requested

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

1. The MAH should provide the case report for the patient who experienced a gastroenteritis and explain the causality assessment.
2. The MAH should provide the Appendix 16.2.6 where non treatment requiring bleeding episodes per subjects are described.

MAH responses to Request for supplementary information

1. The MAH should provide the case report for the patient who experienced a gastroenteritis and explain the causality assessment.

MAH's response:

As this is a non-serious adverse event, then no specific safety case report is available. The adverse event form for this adverse event was provided by the MAH.

The case concerned a 3-year old girl who experienced a mild, non-serious adverse event of gastroenteritis. She has recovered from the adverse event and the rFXIII dose was not changed as a consequence of the adverse event. The adverse event was assessed to be probably related by the investigator. Based on the medical history of the patient, temporal relationship (22 days after rFXIII

dosing), the severity and seriousness of the event as well as young age of the patient, Novo Nordisk does not consider this specific case to be of any safety concern.

Assessor's comment

The non serious event of gastroenteritis (vomiting) observed in a 3 year old child 22 days after last dose, was ticked as probably related to NovoThirteen by the investigator. However the assessor concurs with the MAH's opinion that this case does not raise any concern. This event seems unlikely related to NovoThirteen.

2. The MAH should provide the Appendix 16.2.6 where non treatment requiring bleeding episodes per subjects are described.

MAH's response:

The Appendix 16.2.6 was provided.

Assessor's comment:

14 non treatment requiring bleeding episodes happened in the 6 subjects in which 11 were traumatic. These circumstances seem normal in view of the age of children and do not suggest a product inefficiency.

4. Rapporteur's overall conclusion and recommendation

☒ Fulfilled:

All the issues are considered resolved.