

CLINICAL PHARMACOLOGY BLA REVIEW

Division of Hematology
Office of Blood Review & Research

BLA: 125398 (re-submission)

Product: Novo Nordisk recombinant Factor XIII (A subunit)

Indication: Congenital factor XIII A-subunit deficiency

Sponsor: Novo Nordisk

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Reviewer: Iftekhhar Mahmood, Ph. D.

RPM: Jiahua Qian

Through: Basil Golding, M.D.

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Study# 2: A phase 3b trial investigating the pharmacokinetics and safety profile of a single intravenous dose of rFXIII in pediatric (1 to less than 6 years old) subjects with congenital FXIII A-subunit deficiency (Study #F13CD-3760). 10

INTRODUCTION

Congenital coagulation factor XIII (FXIII) deficiency is a rare, autosomal recessive bleeding disorder with an estimated prevalence of 1 per 2 to 5 million individuals. It is estimated that approximately 100 patients in the US and another 300–500 patients worldwide are diagnosed with this deficiency. Both genders are equally affected. There are two broad phenotypic classes of congenital FXIII deficiency, either affecting the A-subunit or the B-subunit of FXIII. Approximately 95% of all known cases of congenital FXIII deficiency are due to mutations in the gene encoding the catalytic A-subunit. In either subtype of FXIII deficiency, the affected individuals have an increased tendency to bleed, there being a high rate of severe and life-threatening bleeding episodes such as intracranial hemorrhage. Recombinant FXIII (rFXIII) is

thus being developed to provide a safe and effective replacement therapy for patients with FXIII A-subunit deficiency.

The FXIII molecule exists in two forms. The plasma form is a heterotetramer (A₂B₂) composed of two A subunits and two B subunits held together by strong non-covalent interactions. The intracellular form, present in platelets, placenta, spleen, and macrophages, is a homodimer (A₂) composed to two non-glycosylated A subunits only. Both forms are produced as zymogens (i.e., inactive enzymes of “proenzymes”) that require local activation by thrombin and calcium for full activity. Recombinant FXIII is supplied as an A-subunit homodimer (rA₂) and is identical in structure to the human FXIII A-subunit (A₂).

CLINICAL PHARMACOLOGY LABELING COMMENTS

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

FXIII is the terminal enzyme in the blood coagulation cascade. When activated by thrombin at the site of vessel wall injury, FXIII plays an important role in the maintenance of hemostasis through cross-linking of fibrin and other proteins in the fibrin clot. In plasma, FXIII circulates as a heterotetramer [A2B2] composed of two FXIII A-subunits and two FXIII B-subunits held together by strong non-covalent interactions. The FXIII B-subunit acts as carrier molecule for the FXIII A-subunit in circulation, and is present in excess in plasma. When FXIII A-subunit is bound to FXIII B-subunit [A2B2] the half-life of the FXIII A-subunit [A2] is prolonged. FXIII is a pro-enzyme (pro-transglutaminase), which is activated by thrombin in the presence of Ca^{2+} . The enzymatic activity resides with the FXIII A-subunit. Upon activation, the FXIII A-subunit dissociates from the FXIII B-subunit and thereby exposes the active site of the FXIII A-subunit. The active transglutaminase cross-links fibrin and other proteins resulting in increased mechanical strength and resistance to fibrinolysis of the fibrin clot and contribute to enhance platelet and clot adhesion to injured tissue. Coagulation Factor XIII A Subunit (Recombinant) is a protransglutaminase (rFXIII [rA2] homodimer) and it is structurally identical to the human FXIII A-subunit [A2]. The rFXIII A-subunit binds to free human FXIII B-subunit resulting in a heterotetramer [rA2B2] with a similar half-life to [A2B2]. rFXIII has been shown to be activated by thrombin in the presence of Ca^{2+} . Activated rFXIII has been shown in dose-dependent manner to increase mechanical strength of fibrin clots, retard fibrinolysis and rFXIII has been shown to enhance platelet adhesion to the site of injury. **Thus**, Coagulation Factor XIII A Subunit (Recombinant) has been shown to have the same pharmacodynamics properties in plasma as endogenous FXIII.

12.2 Pharmacodynamics

At present there are no markers that can quantitatively assess the *in vivo* pharmacodynamics of FXIII. The results of standard coagulation tests are normal as it is the quality of the clot that is affected. A clot solubility assay is widely used as an indicator of FXIII deficiency, but the assay is qualitative, and when performed correctly the test is positive only when the FXIII activity in the sample is close to zero.

12.3 Pharmacokinetics

Healthy Volunteers

In a single dose pharmacokinetic study, XX# healthy subjects received 35 IU/kg of rFXIII. Pharmacokinetic parameters (baseline corrected) based on FXIII activity measured by the Berichom® assay are shown in Table XX#.

Please provide all PK parameter estimates in a tabulated form (arithmetic mean with standard deviation). You can also report %CV.

Please recalculate all PK parameters with baseline correction. It does not appear that your reported values in the labeling are baseline corrected.

Please provide the relevance/justification of PK parameters of rFXIII in healthy subjects in the labeling. Is PK of FXIII different or similar in healthy subjects and the patients?

~~In a single dose trial, of 35 IU/kg of rFXIII, in healthy male subjects the following geometrical pharmacokinetic parameters based on FXIII activity measured by the Berichom® assay were estimated. arithmetic mean values and coefficients of variation (CV%) across subjects were calculated to provide estimates for a number of pharmacokinetic (PK) parameters for Novo Nordisk rFXIII. Prior to calculation of PK parameters, the FXIII activity profiles were adjusted for the endogenous FXIII plasma activity at baseline for the individual subjects. Clearance was estimated to be 0.13 mL/h/kg (CV=36.5%), the half life estimate was 11.1 days (CV=64.5%) and volume of distribution at steady state had an estimate of 47.1 mL/kg (CV=24.7%). In addition, the initial baseline adjusted concentration at 30 minutes post dosing was 0.85 IU/mL (CV=24.2%) and the area under the activity curve (AUC) was estimated to be 220.3 IU*h/mL (CV=23.8%) from dosing up to 28 days and 277.6 IU*h/mL (CV=47.2%) from dosing to infinity.~~

Steady State in Patients with Congenital Factor XIII Deficiency

~~In a total number of 23 patients with congenital FXIII A-subunit deficiency, pharmacokinetics of rFXIII characteristics were evaluated over a dosing interval of 28 days during steady state (after dosing with 35 IU/kg or 210 microgram/kg of rFXIII). In a tabulated form please provide steady state PK parameters (baseline corrected). If the PK parameters are comparable following single and multiple dosing then simply state that “At steady state, the pharmacokinetics of rFXIII is comparable with the single dose pharmacokinetics of rFXIII”.~~

Please indicate how steady-state PK differs or does not differ from a single dose?

If the half-life of rFXIII is 13.9 days then please explain why there will be no accumulation after multiple-dosing based on a dosing frequency of 28 days?

~~The FXIII activity profiles were time invariant and exhibited mono exponential decline from 3 days post dose and onwards with a mean $t_{1/2}$ of 13.9 days and a geometrical mean Ctrough of 0.16 IU/mL. The maximal post dose activity reached a geometrical mean level of 0.87 IU/mL. All but two, out of a total of 139 obtained PK samples, achieved FXIII activity levels that were above 0.1 IU/mL, which is demonstrative of adequate haemostatic coverage throughout the dosing interval.~~

Pediatric (Ages 1 to < 6 Years Old)

~~In a pharmacokinetic trial, six children with congenital FXIII A-subunit deficiency were administered a single intravenous dose of 35 IU/kg (210 microgram/kg) NovoThirteen. Please recalculate PK parameters based on baseline correction and report the PK parameters in a tabulated form.~~

~~exposed to one single i.v. dose of NovoThirteen 35 IU/kg. The mean $t_{1/2}$ of FXIII was approximately 16 days (range: 10 to 25 days). In this trial, the mean clearance in children was 0.15 mL/h/kg.~~

The following should be in the clinical section.

~~The trial also looked at safety and efficacy in this population. The single i.v. injection was well tolerated. No thromboembolic adverse events were reported. Results of safety laboratory parameters and other safety related examinations did not indicate clinically relevant~~

RECOMMENDATION/

The applicant has responded to the clinical pharmacology questions satisfactorily and has modified the clinical pharmacology labeling as suggested by the FDA. From clinical pharmacology perspective, this application is approvable.

Iftekhar Mahmood, Ph. D.
Clinical Pharmacology Reviewer
Division of Hematology
Office of Blood Review & Research

Basil Golding, MD
Division Director, Division of Hematology
Office of Blood Review & Research

Study #1

Study Title: A multi-center, open-label, single-arm, and multiple dosing trial on safety of monthly replacement therapy with recombinant factor XIII (rFXIII) in patients with congenital factor XIII deficiency (Study #F13CD-3720).

At the end of the review conference with the Food and Drug Administration (FDA) on March 15, 2012, it was concluded that additional data should be provided showing entire PK profiles at steady state in patients with FXIII congenital deficiency exposed to routine prophylaxis dosing schedule (once monthly). In a follow-up telephone conference 11, 2012 the FDA specifically requested the repeat-dose PK to be obtained from 9 patients identified from the F13CD-3720 trial. Novo Nordisk had a post-marketing commitment in the European Union (EU) to provide full steady state PK profiles from at least 5 patients. Consequently, a global amendment to the protocol was made to evaluate rFXIII steady-state PK profiles. Hence, patients were offered the possibility to participate in a PK sampling session over a period of 1 month.

The primary objective of the trial was to evaluate the safety of rFXIII when used for prevention of bleeding episodes and for treatment of breakthrough bleedings in FXIII congenital deficiency patients. The F13CD-3720 trial is an extension to the previously completed F13CD-1725 trial. Another objective of this investigation was to describe the pharmacokinetics (PK) of rFXIII at steady-state in patients with FXIII congenital deficiency exposed to at least two administrations of rFXIII, as part of a once monthly prophylaxis dosing schedule. In this study, patients received at least 10 injections of rFXIII and varied from patient to patient (maximum number of rFXIII injection was 50 in a patient).

This was a multi-center, multi-national, open-label, single-arm, repeat dose phase 3b trial in patients with FXIII congenital deficiency. There were 23 subjects in this study (5 females and 18 males, 7-58 years of age, 22-100 kg of body weight). Out of 23 subjects, 8 subjects were from F13CD-3720 trial and 15 subjects were later included in the study. The patients received a monthly (28 ± 2 days) intravenous (IV) injections of rFXIII (35 IU/kg). For each patient the PK session started at a regular dosing visit during which the standard pre-dosing procedures for such visit was performed. Blood samples for PK assessments were collected at the following time points: Pre-dose (immediately prior to dosing), 1 hour, 2 hours, 3, 7, 14, 21 and 28 days post-dose. At each PK sampling time point, information regarding adverse events (AEs) and bleeding episodes were collected. The PK parameters were calculated using non-compartmental method, without prior baseline adjustment. The calculated PK parameters were based on the data obtained from the Berichrom activity assay.

The results of the pharmacokinetic study are summarized in Table 1 and Figure 1. This study does not indicate if the pharmacokinetics of rFXIII at steady state is different than a single dose.

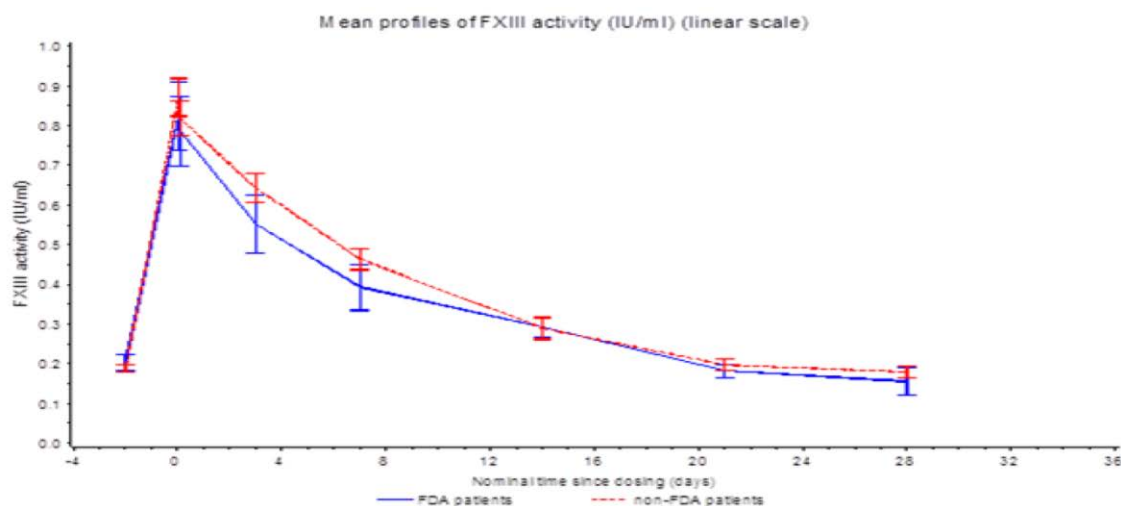
Table 1: Pharmacokinetic parameters of FXIII at steady state (n = 23)
(Baseline un-corrected)

PK Parameters	Values
AUC _(0-28 days) (IU x hr/mL)	240 ± 49
AUC _(0-infinity) (IU x hr/mL)	
CL (mL/hr per kg)	0.15 ± 0.03
Half-life (hrs)	334 ± 83 (13.9 days)
V _{ss} (mL/kg)	73 ± 25

Table 2: Pharmacokinetic parameters of FXIII at steady state (n = 23)
(Baseline corrected)

PK Parameters	Values
AUC _(0-28 days) (IU x hr/mL)	119 ± 40
AUC _(0-infinity) (IU x hr/mL)	128 ± 41
CL (mL/hr per kg)	0.33 ± 0.11
Half-life (hrs)	122 ± 62 (5.1 days)
V _{ss} (mL/kg)	62 ± 23

Figure 1: Concentration-time profile of rFXIII in patients (at steady state)



The PK results indicate a mono-exponential decline in FXIII levels, following first-order elimination with a mean half-life of 13.9 days. The mean FXIII activity levels were above 0.1 IU/mL at all but two time points. There were only two samples from two different patients

(Patient (b) (6) and Patient (b) (6) displaying individual FXIII activity levels below the minimum target level of 0.1 IU/mL, during the entire PK session (not evident from the above mean plot). Overall, mean C_{trough} FXIII activity level, 28 days post-dose, was similar to the mean pre-dose activity level (0.173 IU/mL vs. 0.193 IU/mL, respectively).

Study #2

Study Title: A phase 3b trial investigating the pharmacokinetics and safety profile of a single intravenous dose of rFXIII in pediatric (1 to less than 6 years old) subjects with congenital FXIII A-subunit deficiency (Study #F13CD-3760).

The trial was conducted at five sites, located in UK (2 sites), Israel (1 site) and the US (2 sites). The primary objective of the study was to characterize the pharmacokinetics (PK) of rFXIII in pediatric patients (1 to less than 6 years old) with congenital FXIII A-subunit deficiency following a single intravenous (IV) dose.

This trial was a multi-national, open-label, single-dose trial in which 35 IU/kg rFXIII was administered as an IV injection (at a rate not exceeding 1-2 mL per minute) to pediatric subjects (1 to less than 6 years old) with congenital FXIII A-subunit deficiency.

Six young children with congenital FXIII A-subunit deficiency (three boys and three girls) participated in the study. The mean age was 2.7 years (range: 1 to 4 years). Three children were Asian, two children were White and one child was African American. The mean weight was 16.4 kg (range: 13.7-23.2 kg).

All children had been on monthly prophylactic treatment with a FXIII containing product (Fibrogammin®P/Corifact®) prior to inclusion in the trial, receiving their last dose of their previous prophylactic treatment approximately four weeks prior to the single dose of rFXIII 35 IU/kg. Blood samples were taken pre-dose, at 30 minutes, 24 hours, and days 7, 14, 21 and 30. Concentrations of FXIII activity were measured by Berichrom assay.

Pharmacokinetic parameters of FXIII were calculated by non-compartmental analysis. Half-life of FXIII was calculated using data till day 21. Prior to calculation of AUC, the baseline level of FXIII activity was to be subtracted from all post-dose values. However, baseline adjustment was not conducted and according to the sponsor, the baseline level (pre-dose at visit 2) was not representative for the endogenous FXIII level of the patients, and subtraction of the baseline levels would render invalid results. Instead, it was assumed that a steady state has reached.

The pharmacokinetic parameters are summarized in Table 1. Mean half-life of FXIII was 16 days, with individual values ranging from 10 to 25 days. Mean clearance of FXIII was 0.15 mL/hr/kg, with individual values ranging from 0.13-0.17 mL/hr/kg. The PK parameters of FXIII in children are shown in the following Table. The mean concentration-time plot of FXIII is shown in Figure 1. Based on, baseline un-corrected PK, there is no difference in the PK of FXIII between adults and children 1-4 years of age. A further evaluation will be done with baseline corrected PK between these two age groups.

Table 1: Pharmacokinetic parameters of FXIII in children (1-4 years)
(Un-corrected baseline)

PK Parameters	Values
AUC _(0-30 days) (IU x hr/mL)	250 ± 31
AUC _(0-inf) (IU x hr/mL)	359 ± 61
CL (mL/hr per kg)	0.15 ± 0.02
Half-life (hrs)	378 ± 129 (15.75 days)
V _{ss} (mL/kg)	90 ± 31

Table 1: Pharmacokinetic parameters of FXIII in children (1-4 years)
(Corrected baseline)

PK Parameters	Values
AUC _(0-30 days) (IU x hr/mL)	103 ± 31
AUC _(0-inf) (IU x hr/mL)	108 ± 32
CL (mL/hr per kg)	0.41 ± 0.2
Half-life (hrs)	171 ± 65 (7.1 days)
V _{ss} (mL/kg)	61 ± 41

Figure 1

