

MEMORANDUM



Department of Health and Human Services
Public Health Service
United States Food and Drug Administration
Center for Biologics Evaluation and Research



Pharmacology / Toxicology Review

To: File (STN 125398/0)

From: La’Nissa A. Brown-Baker, Ph.D., Pharmacologist, Division of Hematology
NovoThirteen™ (DH)/OBRR

Through: Iftekhar Mahmood, Ph.D., Team Lead, Pharm/Tox Group, DH/OBRR

Subject: Filing of Final Review of Pharm/Tox Information in STN 125398/0 - Original
Biological License Application for NovoNordisk’s Recombinant human Factor
XIII subunit A (rhFXIII A), NovoThirteen™

This memorandum is the final pharmacology/toxicology review of the non-clinical studies submitted in the original biological license application (BLA) for STN 125398/0 recombinant human factor XIII-homodimer subunit A (rhFXIII A) named NovoThirteen™. This summary is based on review of the pharmacology and toxicology information presented in the BLA, and the clinical experience with NovoThirteen™. The review of non-clinical studies indicates that the information provided for non-clinical evaluation of the product is complete corroborating current clinical data and no outstanding issues are indicated at this time.

Cross Reference: IND 10674 and BB-IND (b) (4)

Review Contents:

- I. Background
- II. Proposed Use and Doses
- III. Recommendations
- IV. General Comments for Non-clinical Program in STN 125398
- V. List of Non-clinical Studies in STN 125398
- VI. Summary Table of Pertinent Non-clinical Studies in STN 125398
- VII. Summary Review Pertinent Non-clinical Studies in STN 125398

I. Background

Congenital Factor XIII deficiency is a rare autosomal recessive disease usually associated with a severe bleeding diathesis. Factor XIII is an enzyme of the coagulation system that cross-links fibrin by activating thrombin. Factor XIII deficiency is the rarest of all coagulation factor deficiencies and is also known as Fibrin Stabilizing Factor deficiency diagnosed by coagulation screening tests and detailed family history. The incidence of FXIII deficiency is about 1 in 2-5

million people. Historical data demonstrates that FXIII replacement therapy is the most widely utilized and effective therapy for this congenital deficiency.

NovoNordisk has manufactured NovoThirteen™, a recombinant human FXIII homodimer A subunit concentrate (rhFXIII A), indicated for prophylaxis treatment of congenital FXIII deficiency. Common side effects following FXIII therapy include anaphylactic reactions, inhibitor development, and thromboembolic events. Nevertheless, the benefits of replacement FXIII therapy far outweigh the risks. The long biological half-life of NovoThirteen™ results in approximately once a month dosing in congenital patients and invariably improves the quality of life for patients with prophylaxis use.

NovoThirteen™ is the first yeast (b) (4) coagulation factor requested to be approved for congenital treatment; in this case, for FXIII deficiency. Throughout the development of NovoThirteen™ (rhFXIII A) there have been various changes and modifications to the manufacturing and production of the final drug product. The sponsor has submitted data to present bridging pre-clinical, clinical, and chemistry, manufacturing, and controls (CMC) findings to demonstrate an adequate comparability and safety profile between the new final formulation of rhFXIII A manufactured in house at NovoNordisk, with that manufactured by former contractor, (b) (4) (a major manufacturing change→ facility change) without any changes to the process. Because recombinant human FXIII A (rhFXIII A) is manufactured from yeast-(b) (4) cells, the prophylaxis and likely off-label use of the product may present concerns for immunogenicity and potential adverse events.

II. Proposed Use and Doses

Recombinant Human Factor XIII A concentrate will be administered bolus intravenously as prophylactic therapy at ~35 U/kg body weight monthly (10-40 U/kg) to congenital patients. The dose and frequency will be determined by treating physician and tailored to plasma levels of each patient, approximately once every 4-6 weeks, for prophylactic treatment of FXIII deficiency.

III. Recommendations

Based on review of the pharmacology and toxicology information presented and clinical experience with NovoThirteen™, I recommend filing of this Biological License Application (BLA) STN125398/0 NovoNordisk's Recombinant human Factor XIII subunit A (rhFXIII A), NovoThirteen™. There are no requests for additional non-clinical information, is not indicated at this time. Also, there are no outstanding issues at final review of this BLA. The non-clinical review indicated some concerns related to product use including immunogenicity, local tolerance, and alterations in hematology panel. These safety concerns will continue to be monitored as a post marketing commitment (PMC) in Phase IV clinical trials.

IV. General Comments for Non-clinical Program in BLA STN 125398

- There were major manufacturing changes and modifications to rhFXIII A throughout the development and clinical trials that were linked based on biocomparability and bridging studies in the pre-clinical program.
- The immunogenicity from rhFXIII A use remains a major concern based on the use of yeast-recombinant production system, formation of neutralizing antibodies in non-clinical studies (monkeys), and evidence of four out of 41 patients developing antibodies during clinical trials following product use.

- There were no special toxicity studies to examine or predict the effect of yeast recombinant production system.
- It is important to note that throughout the pre-clinical program, there were various rhFXIII A doses tested up to 143X single anticipated clinical dose (30 mg/kg in monkeys acutely dosed) and up to 70X multiple anticipated clinical dose (15 mg/kg daily for 4 weeks repeatedly in rodents). The anticipated clinical dose is 35 U/kg body weight monthly (10-40 U/kg) for congenital patients.
- There is extensive pre-clinical data on rhFXIII A in rodents, rabbits, dogs and monkeys with similar results and findings.
- Relevant safety concerns include immunogenicity (formation of neutralizing antibodies), local tolerance from irritation at injection sites, thrombogenicity, and coagulation factor consumption as indicated in both pre-clinical and clinical studies.
- There were no juvenile, developmental & reproductive toxicity, carcinogenicity, genotoxicity, or mutagenicity studies performed on NovoThirteen™.

V. List of Non-Clinical Studies in BLA STN 125398

Study Report (b) (4) **FXIII-0025** - The Binding of FXIII to Endogenous FXIII B of Mouse Rabbit, Dog, Monkey and Human Plasma

Study Report (b) (4) **FXIII-0024** – Activity of rFXIII in (b) (4) Monkey and Human Plasma

Study Report (b) (4) **FXIII-0063** - In Vitro Effects of rFXIII and rFXIII A on Plasma

Study Report (b) (4) **051125** – Effect of rFXIII on clot resistance to Fibrinolysis

Study Report (b) (4) **-FXIII-0058** – In vivo Plasma Protein Cross-linking by rFXIII in (b) (4) Monkeys

Study Report (b) (4) **-10352** - Evaluation of the Influence of Recombinant Human FXIII (rFXIII) on Fibrinolytic Resistance in a tPA-induced Re-bleed model in the Rabbit

Study Report (b) (4) **100501** – Combined Effect of rFXIII and rFVIIa in a rabbit model of tissue plasminogen activator enhance liver bleeding model

Study Report (b) (4) **050520** - FVIIa Combination Therapy Thromboelastography evaluation of whole blood form normal donors and patients undergoing stem cell transplantation and cardiac surgery

Study Report (b) (4) **FXIII-0014** - rFXIII-A2 Toxicity on Cultured (b) (4)

Study Report (b) (4) **-FXIII- 0015** - Up-regulation of adhesion molecules by activated and non-activated rFXIII

Study Report (b) (4) **-FXIII0016** - Inflammatory cytokine release in the ex vivo whole blood assay with rFXIII; thrombin (A2) and non-activated

Study Report (b) (4) **-FXIII-0017** - In vitro, live cell binding of recombinant FXIII to endothelial-fibroblast- smooth muscle and bone marrow derived cell lines with (b) (4)

Study Report (b) (4) **-FXIII-0018** - Recombinant FXIII binding to Human Blood cells by (b) (4)

Study Report (b) (4) **-10351** - Influence of Recombinant Human FXIII (rFXIII) on Platelets Stimulated by Cotton Threads Incorporated into an Arteriovenous (AV) Shunt

Study Report (b) (4) **-1112-010** – Pilot Study of (b) (4) in (b) (4) Monkeys after Extracorporeal Blood Circulation

Study Report (b) (4) **-1112-011** - Toxicology Study of Intravenous rFXIII Injection (1000 U/kg) to Male (b) (4) monkeys after Extracorporeal Blood Circulation

Study Report (b) (4) **-1112-013** – Toxicology Study of Intravenous rFXIII injection (1000 U/kg) to male (b) (4) Monkeys after Extracorporeal Blood Circulation

Study Report (b) (4) **-10323** – In vitro verification of Non-cross Reactivity of Recombinant Factor XIII with Heparin and Protamine

Study Report NN205070 – rFVIIIa and FXII Single Dose administration Non-GLP Toxicity Study in the (b) (4) Monkey Followed by a Three Day Observation Period

Study Report NN205148 – rFVIIa and rFXIII Single Dose Intravenous Administration GLP Toxicity Study in the (b) (4) Monkey Followed by a Three Day Observation Period

Study Report NN2061000 - rFVIIa rFXIII: Effects of General Haemodynamics in Anaesthetised, (b) (4) Primates

Study Report (b) (4) **1224-175** – Pharmacokinetics of rFXIII in Naïve Female (b) (4) monkeys following Intravenous Injection 1.0 or 5.0 mg/kg or repeat Dose of 5 mg/kg rFXIII (b) (4) 1224-175, Non-GLP)

Study Report (b) (4) **1241-175** - Pharmacokinetics of rFXIII in Naïve Female (b) (4) Monkeys Following Intravenous Injection 1.0 or 5.0 mg/kg or repeat Dose of 5 mg/kg rFXIII (b) (4) – 12541-175, GLP)

Study Report NN207399 - Factor XIII: Single Dose Pharmacokinetics Study in Juvenile and Mature (b) (4) Monkeys following a Single Intravenous Injection 0.5, 1.0, 5.0 mg/kg rFXIII (b) (4) 1224-175, GLP)

Study Report 7333-101-A- Pharmacokinetics of 125I-rFXIII administered to Male and Female (b) (4) monkeys

Study Report 7333-101-B- Elimination of 125-I Recombinant Factor XIII (rhFXIII) Following Intravenous Administration to Monkeys

Study Report (b) (4) **1220-175** A Pilot Non-GLP Acute Intravenous Toxicity Study of rFXIII in Adult Female (b) (4) Monkeys

Study Report (b) (4) **1228-175** An Acute Intravenous Toxicity Study of rFXIII in Young Adult Female (b) (4) monkeys

Study Report NN209517- 5-Day Intravenous (Bolus) Administration Range-Finding Study in the Rat with a 3 Day Observation Period

Study Report NN209502 – 28 Day Intravenous (Bolus) Administration Toxicity Study in the Rat with Two-Comparator Arms followed by a 14-Day Treatment Free Period

Study Report (b) (4) **1266-175** A Repeat Dose Toxicity Study of rFXIII Administered by Intravenous Infusion to Male and Female (b) (4) monkeys with a 4-week Recovery period

Study Report (b) (4) **-1249-175** – A Pilot Acute Toxicity Study of Intravenous rFXIII in Young Adult Male and Female (b) (4) Monkeys

Study Report (b) (4) **-1394-175** – A 14-Day Toxicity Study of rFXIII Administered by Intravenous Bolus Injection One Daily to (b) (4) Monkeys with 30-Day Recovery Period

Study Report (b) (4) **1266-175** – A Repeated Dose Toxicity Study of rFXIII Administered by Intravenous Infusion to Male and Female (b) (4) Monkeys with 4-week Recovery Period

Study Report NN205255 – NN1841 Recombinant FXIII: 27-Week Intermittent Intravenous Administration Toxicity Study in the Monkey Followed by an 8-Week Reversibility Study

Study Report NN205496 - Local Tolerance in Rabbits 4 days after intravenous perivenous and intra-arterial injection

Study Report NN209504 - Local Tolerance in Rabbits 4 days after intravenous perivenous and intra-arterial injection

There were thirteen preliminary special or other Toxicity studies completed using NovoThirteen™ including dose ranging finding studies and comparative analysis between batches of FXIII. In addition, it is noted that NovoThirteen™ was originally developed by (b) (4) and has undergone significant manufacturing/production changes to improve product and reduce adverse effects associated with predecessor product use. The non-clinical label for NovoThirteen™ will be complete as a Post Label Review (PLR) after the sponsor addresses outstanding clinical response (CR) issues.

All pre-clinical study reports are finalized and appear complete for adequate review of this application. Non-clinical studies using the predecessor form of NovoThirteen™ were review but the results are not included in this summary. These review data can be referenced in IND 10674 and BB-IND (b) (4)

Below is a listing of preliminary, *in vitro* pharmacokinetics, and other toxicity studies using NovoThirteen:

- Study Report** (b) (4) **051125** – Effect of rFXIII on clot Resistance to Fibrinolysis
- Study Report** (b) (4) **050520** – FVIIa Combination Therapy. Thromboelastography Evaluation of Whole blood from normal donors and patients undergoing stem cell transplantation and cardiac surgery
- Study Report** (b) (4) **100501** – Combined Effect of rFXIII and rFVIIa in a Rabbit Model of Tissue Plasminogen Activator Enhanced Liver Bleeding
- Study Report** (b) (4) **2642-100** - 14 Days Intravenous Toxicity Study of FXIII in Dogs
- Study Report** (b) (4) **2642-102** - 14 Days Intravenous Toxicity study of FXIII in Dogs
- Study Report** (b) (4) **-002-02** – A Dose Range Finding Study of Recombinant Factor rFXIII Administered as a Single intravenous Infusion in Female (b) (4) Monkeys
- Study Report** (b) (4) **91003** – rFXIII Rat Toxicology of batch F249124 rFXIII
- Study Report** (b) (4) **92001R** – FXIII Rat Toxicology 2: Toxicity of Batch F249127 rFXIII
- Study Report** (b) (4) **92002** – rFXIII Rat Toxicology 3: Toxicity of lower doses of Batch F249124 rFXIII
- Study Report** (b) (4) **92003-** rFXIII Rat Toxicology 4 and 5: Toxicity of Batches F249124 and F249130 after removal of rFXIIIa
- Study Report** (b) (4) **92004** – rFXIII Rat Toxicology 6: Toxicity of Batch F249124 after removal of rFXIIIa
- Study Report** (b) (4) **92005** – Toxicity in Rats of rFXIII spiked with rFXIIIa
- Study Report** (b) (4) **2006-** Acute Toxicity of a series of rFXIII batches
- Study Report** (b) (4) **92007** – Acute Toxicity of a series of rFXIII batches
- Study Report** (b) (4) **92008** – Toxicity of Neat rFXIII in Rats
- Study Report** (b) (4) **92011** – Toxicity of Activated rFXIII in Rats: A Summary

VI. Summary Table of Relevant Non-Clinical Studies in STN 125398

Study number	Purpose	Species	Dose(s)	Study Observations
(b) (4)-FXIII-0058	Pharmacodynamics	Monkey	1-30 mg/kg	Crosslinking of FXIII occurs in blood circulation of monkeys after i.v. injection of rhFXIIIa
(b) (4)-10352	Pharmacodynamics	Rabbit	0.4 mg/kg	N=6, rhFXIIIa effect in tPA induce bleeding (improved) in rabbits based on time to lysis of blood clot formed
(b) (4)100501	Pharmacodynamics	Rabbit	0, 0.1, 1, or 3 mg/kg	tPA enhance liver bleeding reduced by rhFXIIIa & rFVIIa treatment
(b) (4) 1112-011	Safety Pharmacology Cardiovascular	(b) (4) monkeys	0, 2.1, or 7.1 mg/kg	rhFXIIIa vs. placebo after heparin --> protamine to increase FXIII activity, N=10, There was no cardiotoxicity noted after 2 hrs. bolus injection w/ 6 h observation
(b) (4) 1112-013	Safety Pharmacology	(b) (4) monkeys	1.0 mg/kg	rhFXIII vs. placebo after i.v. injection were dose dept. rhFXIII activity (efficacy) 6 hrs
NN205070	Acute Toxicology	(b) (4) monkeys	0.34, 1.112, 5.6, or 16.8 mg/kg rFXIII	rFVIIa & rhFXIIIa (1.6 + 5.6 mg/kg) was NOAEL w/3 d observation N=1M/1F four doses tested; highest dose (5.0 FVIIa + 15.0 FXIII mg/kg) = 2 mortalities (DIC)
NN205148	Acute Toxicology (GLP)	(b) (4) monkeys	3.5, 7, 14, 10.5, 3.5, 10.5 mg/kg rFXIII	rFVIIa & rhFXIIIa (doses varied) w/ 2 +7 mg/kg respectively LOAEL, ~ N=3 w/ observation period Biomarkers tested = increased FIB, DDM & TAT levels, thrombi & necrosis in high dose gr. (>3.5mg/kg FXIII)
NN206100	Acute Toxicology (Cardiovascular)	(b) (4) monkeys	0, 1.75, 3.5, or 7 mg/kg rhFXIIIa	rFVIIa & rhFXIIIa for ECG & hemodynamic effects after anesthesia N=4M
(b) (4)-FXIII-0024 (b) (4)-FXIII-0063	Safety Pharmacology	Human plasma vs. (b) (4) plasma	10 mg/mL Formulation	Compared thrombin activated FXIIIa vs. non-proteolytically activated FXIIIa cross-linking (dose-responsive) were similar post-dose activated by plasma
(b) (4) 1394-175	Repeat dose toxicity	(b) (4) monkeys	0, 0.3, 3 or 6.0 mg/kg	Animals (n=3-5/sex/gr.) were dose daily for 2 wk + 4 wk recovery NOAEL = 6.0 mg/kg all doses tolerable; FXIII subunit A & B are consumed post-dose
(b) (4) 1241-175	Acute & Repeat Pharmacokinetics	(b) (4) monkeys (Naïve)	1.0 or 5.0 mg/kg (acute) Only 5.0 mg/kg (repeat)	Preliminary study for cardiovascular and CNS system safety pharmacology and PK ((b) (4) for A and AB subunits)
NN207399	Acute	(b) (4)	0.5, 01.0, 5.0	Monkeys (n=6/sex/gr.) dosed & sampled for FXIII, subunit A & AB by

	Pharmacokinetics	monkeys (Mature vs. juvenile)	mg/kg	(b) (4) & chromogenic assays up to 504 hr. (22 days) juveniles had lower activity for FXIII A & AB subunits (AUC) but no diff. in B levels ; no sex diff.
7333-101-A&B	Pharmacokinetics & elimination	(b) (4) monkeys	0.5 or 5 mg/kg	Monkeys (n=2/sex) were dosed & sampled at or 72 hr. w/ radiolabeled predominantly urine excretion dose-dept. over time
NN205904	Local Tolerance	Rabbits	5 mg/kg	i.a., p.v. and i.v. injection w/ 4 d observation of rFXIII vs. vehicle product was tolerable but notable difference in rFXIII administration vs. vehicle
NN20255	Repeat dose toxicity	(b) (4) monkeys	0, 1, 3, or 10 mg/kg	Animals (n=3-5/gr) treated for 27 wk. bi-weekly dosing NOAEL = 3 mg/kg, neutralizing cross-reacting antibodies by Wk. 13 in all test gr.'s FXIII activity increased
NN209517	Dose range finding	rats	5 or 15 mg/kg	N=10/sex/tox gr. & n=12/sex/TK gr. Dosed 5 d w/ 3 d recovery 1 mortality (control), 1 air emboli (1 M high 15 mg/kg)
NN209502	Repeat Dose Toxicity	Rats	0, 1, 5, or 15 mg/kg	Rats (n=10/sex, n=3/recovery) were dosed daily for 28 d w/ 2 wk recovery for comparative analysis for rhFXIII from NN vs. (b) (4) facilities, 1 mortality (control), products comparable & tolerable,
(b) (4) 1266-175	Repeat Dose Toxicity	(b) (4) monkeys (juvenile vs. mature)	0, 5, 8, 12.5 mg/kg	Monkeys (n=3-5/sex/gr.), lymphoid hyperplasia in all F high dosed gr. NOAEL = 5mg/kg, PK by (b) (4)

Abbreviations

Wk. = week(s)	d = day(s)	gr. = group	NN = NovoNordisk
i.v. = intravenous	p.v. = paravenous	M = male	F = female
diff. = difference	w/ = with	FIB = fibrinogen	T = total number
tPA = tissue plasminogen activator		PK = pharmacokinetics	Ret = reticulocytes
dept. = dependent		TK = toxicokinetics	hr. = hour(s)
AUC = area under the curve		NOAEL = no observed adverse effect level	
TAT = thrombin anti-thrombin III complex		LOAEL = lowest observed adverse effect level	

VII. Summary Review of Pertinent Non-clinical Studies in STN 125398

Study Report NN209517 - 5 Day Intravenous (Bolus) Administration Range-Finding Study in the Rat with a 3 Day Observation Period

The aim of this study is to determine the therapeutic range of the new formulation of rhFXIII in rats. Rats (n=10/M&F toxicity and n=12/M&F toxicokinetics, T= 54 rats) were dosed vehicle (control), 5 mg/kg (~835 IU-20x clinical dose) and 15 mg/kg (~2505 IU-70X clinical dose) for five days with 3-day recovery for toxicokinetics. Limited histopathology was taken (lungs, brain, kidneys), complete serum and clinical chemistry panel, clinical observations, urinalysis, body weight, etc. monitored. One animal was euthanized on Day 5 in toxicokinetics high dose group (1F, animal 51, 15 mg/kg rhFXIII) for poor condition, likely treatment related, although sponsor claims otherwise. The observed air emboli in the lung was considered to be related to the intravenous injection procedure and not related to administration of rhFXIII (1 M animal 15, 15mg/kg). There was increased severity of nephropathy (although incidence rates were the same between groups) in treated animals than vehicle animals and local irritation associated with product use. FXIII activity was sex (higher in females), time, and dose dept. in animal tested as expected. It appears that rhFXIII does not cause overt toxicity in acute testing but may cause some adverse responses related to focal nephropathy, lung alterations (inflammation, macrophages) and local irritation at high doses and multiple dosing (repeat use). Repeat dose toxicity studies have been reviewed to substantiate these findings. These results should be considered for inclusion in clinical monitoring signs.

Study Report NN209504 - Local Tolerance in Rabbits 4 days after intravenous perivenous and intra-arterial injection

The aim of this study is determine if rhFXIII will be well tolerated in local injection sites in rabbits followed by 4 days observation. Rabbits (n = 4/gr.) were dosed 835 IU (5 mg/kg) in left ear and vehicle (0.05 ml/kg) in right ear by various routes of administration: intra-arterial (i.a), paravenous (p.v), or intravenous (i.v) which is the intended clinical route of administration. Animals tested for p.v. and i.a. demonstrate similar results between test articles over course of the study. However, the scores for intravenous route of administration were notably different for the drug product (rhFXIII) vs. vehicle. Animals dosed i.v. scored (severity assessment) between 1-2 on average in rhFXIII group vs. 0-1 for the vehicle group. Due to the small sample sizes of groups, it is concluded that the test article is not as tolerable as vehicle in the intended route of administration. Of note, clinical signs of swelling, irritation, and hemorrhage were noted related to use of rhFXIII administration (local site). These findings should be considered as a part of clinical monitoring. These results were consistent with previous formulation, tested in repeat dose toxicity studies for other animals.

Study Report 209502 – 28 Day Intravenous (Bolus) Administration Toxicity Study in the Rat with Two Comparator arms Followed by a 14 Day Treatment-free Period

The aim of this study is to evaluate the repeat dose toxic effects of rhFXIII in rats to establish adequate safety profile for prophylaxis use. Rats (n=10/sex/group, 3/recovery and n = 5 control) were dosed vehicle (control buffer) 1 or 5 mg/kg rFXIII NovoNordisk drug substance (NN) or rhFXIII (b) (4) and 15 mg/kg NN rhFXIII. There was one mortality of a male animal in control vehicle group on Day 26 (poor condition likely due to handling and sampling procedure). There were no overt toxicities noted in this study. There appeared to be a trend for alteration in coagulation consumption factors including fibrinogen (FIB - decreased), reticulocytes (RET - increased), etc. that were dose-dependent in effect. There was a statistically significant decrease

in white blood cells (WBC) in both rhFXIII groups for females only (5 mg/kg (b) (4) 1 mg/kg NN, 15 mg/kg NN). These differences were not dose-dependent or consistent within groups. Microscopically, one male animal given 15 mg/kg/day had a higher severity (slight) of focal nephropathy than the background severity (minimal) observed in vehicle controls. This result was isolated to a single animal. There was antibody formation in all treated groups by day 28 and persisted in all but 2 NN animals and 8 (b) (4) animals after recovery period (effect was not dose dependent and was reversible). All treated animals had decreased fibrinogen levels with no micro/macrosopic pathological findings. Lymphoid hyperplasia post-dose incidences could be linked to positive antibody responses (microscopically noted) likely as a result of animal injection with foreign antigenic properties. Based on comparative analysis between the old formulation and the new formulation of FXIII, the results appear to correlate with previous formulation responses vs. current responses. There were no other changes in clinical observations. This is an audited study report.

Study Report NN205255 – NN1841 recombinant FXIII: 27 week Intermittent Intravenous Administration Toxicity Study in the Monkey Followed by an Eight week Reversibility Period

The aim of this study is to evaluate the repeat dosing long term toxic effect in monkeys to establish the safety profile for prophylaxis use and determine reversibility of product use. Monkeys were dosed control (vehicle buffer, n=5/sex and n=2/sex/recovery group), 1 mg/kg (n=3/sex), 3 mg/kg (n=3/sex), 10 mg/kg (with rhFXIII ((b) (4) Batch (b) (4) for 27 weeks with an eight week treatment free recovery period or 10 mg/kg (n=5/sex & n=2/sex/recovery group) for 13 weeks. The following parameters were monitored during the study: toxicokinetics, necropsy including micro/macrosopic pathology, anti-FXIII antibodies, FXIII activity, complete serum and clinical chemistry panel, clinical observations (clinical signs), urinalysis, body weight, ophthalmoscopy, and food consumption. There were two mortalities in the study: one female in 1 mg/kg group (d 75 [post 6 doses] sacrificed for drastic weight loss [16% in 11 days]→ moribund condition; gastrointestinal lesions [enteritis, microabscesses & parasite infection]) and one male in 10 mg/kg on day 5 post dose (likely circulatory failure --> kidney necrosis; hemorrhage). High dose male animals (10 mg/kg group) had reduced weight gain packed cell volume and reticulocytes compared to all other groups. Anti-FXIII antibodies were present at day 15 as expected due to immune response in all, but in two animals it persisted through treatment-free period. There was no overt toxicities noted in study and all other clinical parameters were within normal range (without statistical significance between groups).

Local irritation at injection site was noted in treatment animals. There appears to be consumption of Ret, FIB and FXIII subunit B following dose-dependent manner.

There was an appearance of interaction between AUC and FXIII that was inversely proportional over time. The antibody development effect on toxicokinetics (AUC) based on FXIII subunit activity (A and/or AB) could not be determined. However, this can not be corroborated due to insufficient group numbers (collected samples missed at times). Furthermore, it appears that there is a trend of FXIII levels fluctuating but gradually decreasing subunit activity over time for both A & B subunits. The NOAEL is 3 mg/kg for this study based on severe adverse events.