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Division / Office	DH /OBRR
Priority Review	No
Reviewer Name	Charles M. Maplethorpe M.D., Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Novo Nordisk Inc.
Established Name	Coagulation Factor XIII A Subunit (Recombinant)
(Proposed) Trade Name	NovoThirteen
Pharmacologic Class	Coagulation Factor FXIII
Formulation(s), including Adjuvants, etc.	Lyophilized white powder with following excipients: sodium chloride, sucrose, polysorbate 20, L-Histidine
Dosage Form(s) and Route(s) of Administration	Lyophilized white powder to be reconstituted with 3.2 mL Sterile Water for Injection (b) (4) intravenous administration
Dosing Regimen	35 IU/kg i.v. monthly
Indication(s) and Intended Population(s)	Routine prophylaxis of bleeding in patients with congenital Factor XIII A-subunit deficiency

Table of Contents

The electronic versions of this document contain hyperlinks that branch to a referenced section of this document, when the CTRL is depressed while the item is clicked on with the computer mouse. To return to the original branch point in the document, press

ALT- ← [ALT – Back Arrow]. 1

Glossary 1

1. Executive Summary 1

2. Clinical and Regulatory Background..... 12

2.1 Disease or Health-Related Condition(s) Studied12

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s).....16

2.3 Safety and Efficacy of Pharmacologically Related Products16

2.4 Previous Human Experience with the Product (Including Foreign Experience)18

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission.....18

2.6 Other Relevant Background Information18

3. Submission Quality and Good Clinical Practices 18

3.1 Submission Quality and Completeness18

3.2 Compliance With Good Clinical Practices And Submission Integrity.....19

3.3 Financial Disclosures19

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines..... 19

4.1 Chemistry, Manufacturing, and Controls19

4.2 Assay Validation19

4.3 Nonclinical Pharmacology/Toxicology.....25

4.4 Clinical Pharmacology32

 4.4.1 Mechanism of Action.....32

 4.4.2 Human Pharmacodynamics (PD).....32

 It can be seen that the 35 IU/kg dose resulted in 1-hour post-dose FXIII activity levels of approximately 1 IU/mL, as measured by the Berichrom assay.32

 It can be seen that there is decreased dose proportionality as FXIII activity values increase toward 1 IU/mL, with loss of dose proportionality at FXIII activities above 1 IU/mL.33

 4.4.3 Human Pharmacokinetics (PK).....34

4.5 Statistical35

4.6 Pharmacovigilance.....35

5. Sources of Clinical Data and Other Information Considered in the Review 35

5.1 Review Strategy35

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review35

5.3 Table of Studies/Clinical Trials36

5.4 Consultations.....37

 5.4.1 Advisory Committee Meeting (if applicable)38

 5.4.2 External Consults/Collaborations.....38

5.5 Literature Reviewed (if applicable)	38
6. Discussion of Individual Studies/Clinical Trials	38
6.1 Trial #1	38
6.1.1 Objectives (Primary, Secondary, etc.).....	38
6.1.2 Design Overview	38
6.1.3 Population	38
6.1.4 Study Treatments or Agents Mandated by the Protocol.....	39
6.1.5 Directions for Use	39
6.1.6 Sites and Centers	39
6.1.7 Surveillance/Monitoring	39
6.1.8 Endpoints and Criteria for Study Success	40
6.1.9 Statistical Considerations & Statistical Analysis Plan	40
6.1.10 Study Population and Disposition	52
6.1.11 Efficacy Analyses	53
6.1.12 Safety Analyses.....	53
6.2 Trial #2	63
6.2.3 Population	63
6.2.4 Study Treatments or Agents Mandated by the Protocol.....	63
6.2.5 Directions for Use	64
6.2.6 Sites and Centers	64
6.2.7 Surveillance/Monitoring	64
6.2.8 Endpoints and Criteria for Study Success	64
6.2.9 Statistical Considerations & Statistical Analysis Plan	64
6.2.10 Study Population and Disposition	64
6.2.11 Efficacy Analyses	67
6.2.12 Safety Analyses.....	67
7. Integrated Overview of Efficacy	68
7.1 Indication #1	68
7.1.1 Methods of Integration	68
7.1.2 Demographics and Baseline Characteristics	68
7.1.3 Subject Disposition	68
7.1.4 Analysis of Primary Endpoint(s)	68
7.1.5 Analysis of Secondary Endpoint(s)	68
7.1.6 Other Endpoints	68
7.1.7 Subpopulations	68
7.1.8 Persistence of Efficacy	68
7.1.9 Product-Product Interactions	68
7.1.10 Additional Efficacy Issues/Analyses	68
7.1.11 Efficacy Conclusions	68
8. Integrated Overview of Safety	68
8.1 Safety Assessment Methods	68
8.2 Safety Database	68
8.2.1 Studies/Clinical Trials Used to Evaluate Safety.....	69
8.2.2 Overall Exposure, Demographics of Pooled Safety Populations	69
8.2.3 Categorization of Adverse Events.....	69
8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials	69
8.4 Safety Results	69
8.4.1 Deaths	69
8.4.2 Nonfatal Serious Adverse Events.....	69
8.4.3 Study Dropouts/Discontinuations	69
8.4.4 Common Adverse Events.....	69
8.4.5 Clinical Test Results	69
8.4.6 Systemic Adverse Events.....	69

8.4.7 Local Reactogenicity.....	69
8.4.8 Adverse Events of Special Interest	69
8.5 Additional Safety Evaluations	69
8.5.1 Dose Dependency for Adverse Events.....	69
8.5.2 Time Dependency for Adverse Events.....	69
8.5.3 Product-Demographic Interactions	69
8.5.4 Product-Disease Interactions.....	69
8.5.5 Product-Product Interactions.....	69
8.5.6 Human Carcinogenicity	69
8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound.....	70
8.5.8 Immunogenicity (Safety)	70
8.6 Safety Conclusions	70
9. Additional Clinical Issues.....	70
9.1 Special Populations.....	70
9.1.1 Human Reproduction and Pregnancy Data	70
9.1.2 Use During Lactation	70
9.1.3 Pediatric Use and PREA Considerations	70
9.1.4 Immunocompromised Patients.....	70
9.1.5 Geriatric Use	70
9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered.....	70
10. Conclusions.....	70
11. Risk-Benefit Considerations and Recommendations.....	70
11.1 Risk-Benefit Considerations	70
11.2 Risk-Benefit Summary and Assessment	72
11.3 Discussion of Regulatory Options.....	74
11.4 Recommendations on Regulatory Actions.....	74
11.5 Labeling Review and Recommendations	74
11.6 Recommendations on Postmarketing Actions.....	74
<u>Appendix 1. Study F13CD-1725 Eligibility Criteria and Schedule of Events Flowchart</u>	
<u>Appendix 2. Factor XIII activity levels, Bleeding events (Efficacy Primary Endpoint), and anti-FXIII antibody results</u>	
<u>Appendix 2.1 PK Data for Corifact® from Study BI71023 2002 in STN125385 [CSL Behring]</u>	
<u>Appendix 3. Treatment Emergent Adverse Events in Study F13CD-1725 by Seriousness and Severity</u>	
<u>Appendix 4. Treatment Emergent Adverse Events in Study F13CD-3720 by Seriousness and Severity</u>	
<u>Appendix 5. Platelet counts, Fibrinogen levels, and RBC counts by Subject for Study F13CD-1725</u>	
<u>Appendix 6. Anti-FXIII Antibody Results for Studies F13CD-1725 and F13CD-3720</u>	
<u>Appendix 7. Pre-Dose to 1-Hour Post-Dose Change in B Subunit Concentration (µg/mL) by 1-Hour Change in FXIII Berichrom Activity by Subject and Study Visit</u>	

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GLOSSARY

1. Executive Summary

Novo Nordisk, Inc. has submitted Biologics License Application STN125398 for Coagulation Factor XIII A Subunit (Recombinant) (NovoThirteen[®]) seeking the following indication:

Routine prophylaxis of bleeding in patients with congenital Factor XIII A-subunit deficiency.

NovoThirteen[®] is not Factor XIII. NovoThirteen[®] is the A subunit dimer [A₂] of human coagulation Factor XIII produced from genetically modified yeast (*Saccharomyces cerevisiae*), and supplied as a sterile lyophilized powder. After reconstitution and intravenous injection, the A subunit dimer combines with free B subunits in the plasma to form a heterotetramer [A₂B₂] that has properties similar to human coagulation Factor XIII. NovoThirteen[®] has transglutaminase activity similar to Factor XIII. The applicant assigns activity units to NovoThirteen[®] as “International Units” using a proprietary assay and a standard that is traceable to the WHO 1st International Standard Factor XIII Plasma (NIBSC code:02/206). One vial of NovoThirteen[®] contains 2500 IU (b) (4).

Regulatory Chronology. IND 10674, the precursor to this BLA, was submitted in September 2002. (b) (4)

[REDACTED]

IND 10674 was placed on clinical hold (February 2006) upon submission of a special protocol assessment (SPA). It was placed on clinical hold again (August 2006) pending submission of a final study report for the repeat-dose (b) (4) monkey study NN205255. Novo Nordisk requested and received a clinical hold for IND 10674 (May 2010) in order to impose review timelines for the review of a submission containing manufacturing changes.

Pediatric Research Equity Act (PREA). PREA does not apply because NovoThirteen[®] received orphan product designation in May 2003.

Congenital Factor XIII Deficiency. This disease is inherited as an autosomal recessive bleeding disorder that is clinically apparent at a frequency of approximately 0.5-1.0 per million births. It may be detected at birth through umbilical bleeding, or later after

investigation of re-bleeding events after apparently successful hemostasis. Bleeds are not frequent (1-2 per year), however they may be life-threatening, including intracranial hemorrhage reported by one-third of subjects not on prophylaxis with a Factor XIII-containing product. In the U.S., routine prophylaxis is the standard of care. Because the disease phenotype is apparent only after plasma Factor XIII activity levels fall below 5% of the normal level, dosing algorithms seek to maintain the plasma Factor XIII level above 5% of the normal level. Inhibitor formation (i.e. clinically-apparent anti-FXIII neutralizing antibody response) is very rare among the congenitally FXIII-deficient population (a publishable event).

STN12398 for Routine Prophylaxis. To support this indication, the following clinical trials conducted under IND have been completed or are ongoing:

- **F13-1663** US (2004) -- Safety and pharmacokinetics of rFXIII in patients with congenital factor XIII deficiency
- **F13CD-1725** (2010) Europe, Canada, US -- Phase 3 efficacy and safety
- **F13CD-3720** (Ongoing) Europe, Canada, US -- Safety extension trial to the phase 3 F13CD-1725 trial

A table of all clinical studies using this product is given in [section 5.3](#).

This review focuses on the pivotal study F13CD-1725. The study design was agreed upon with FDA after a request for a Special Protocol Assessment (SPA) was submitted. Study F13CD-1725 enrolled 41 congenitally FXIII-deficient males and females aged 7-60 years of age at study sites in Europe, Canada and the U.S. After a 4 week run-in period, subjects received intravenous injections of 35 IU/kg NovoThirteen every 3 or 4 weeks for 52 weeks in order to maintain their trough FXIII activity level (by the Berichrom assay) above 5% of the normal level. There was a 4 week follow-up period, followed by entry into ongoing extension study F13CD-3720, which allows for continued treatment with safety monitoring. The following diagram shows the design of the pivotal study F13CD-1725:

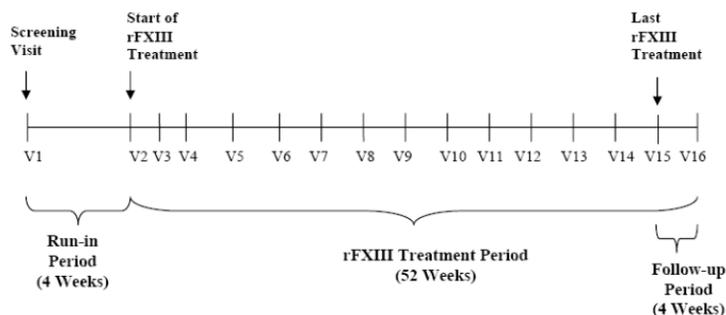


Figure 9-1 Trial Design

Source: Original BLA 125398; Clinical Study Report module 5.3.5.4.3, p.23

Blood samples were drawn pre-dose and 1-hour post-dose at each visit to capture pharmacokinetic and pharmacodynamic data.

The primary endpoint was “rate (number per subject year) of bleeding episodes that required treatment with a FXIII-containing product during the treatment period.”

Data for an external control group (retrospective) were developed based on a questionnaire administered to 92 congenitally Factor XIII-deficient subjects from Australia, Brazil, Europe, Israel, Saudi Arabia, and South Africa [see [section 6.1.9](#)]. Of these 92 subjects, 23 were reported to not be on current FXIII prophylaxis treatment; therefore, the reported bleed frequency from these 23 subjects was used by the applicant to derive an expected bleed frequency of 2.91 bleeds per year for an untreated external control group.

[**N.B.:** After review of the submitted data, it appears that 2 subjects must be removed as outliers (11 and 12 bleeds per year reported, respectively), reducing the expected bleed frequency to 1.62 per year. This was communicated to Novo Nordisk on September 22, 2011, and Novo Nordisk responded in STN125398.09 by defending the inclusion of the data from these two subjects based on expected variability in bleed rates (see [section 6.1.9](#)).]

Results of pivotal study F13CD-1725. Of the 41 entered subjects, there were 8 subjects who withdrew from study F13CD-1725 (3 due to anti-rFXIII antibody response, 2 for pregnancy, 1 due to worsening leucopenia, 1 to avoid blood sampling, and 1 for personal reasons) leaving 33 subjects in the *per protocol* analysis group. [see [Appendix 2](#) for a graphical presentation of efficacy and antibody response outcomes.]

There were 4 subjects who reported 5 bleeds treated with FXIII-containing products. For the full analysis set (41 subjects), the applicant reports a mean bleed rate of 0.048 [95% CI: 0.0094; 0.2501] with a p-value of 0.022 for a no-difference comparison to the external control rate of 2.91 bleeds per subject-year. Therefore, the applicant claims a demonstration of efficacy.

In study F13CD-1725, there were 231 treatment-emergent adverse events reported for 32 subjects [see [Appendix 3](#)]. The most commonly reported events were headache (21 events in 12 subjects), incorrect dosing (14 events in 7 subjects), nasopharyngitis (11 events in 8 subjects) and pyrexia (7 events in 7 subjects). There were 13 adverse events in 9 subjects that were classified by the investigator or sponsor as possibly or probably related to the study agent, as shown in the following table:

Treatment-emergent Adverse Events with Possible or Probable Relation to Trial Product - Full Analysis Set

Subject ID	Age	Preferred Term	Severity	Serious	Latency	Relation	Outcome
(b) (6)	7	Antibody test positive	Mild	Y	14	Probable	Recovered
	25	Pain in extremity	Mild	N	22	Possible	Not Recov.***
	26	Headache	Mild	N	0	Possible	Recovered
	8	Leukopenia****	Mild	N	32	Possible	Recovered

(b) (6)		Neutropenia****	Mild	N	32	Possible	Recovered
	7	Incorrect dose administered	Mild	N	0	Probable	Recovered
		Incorrect dose administered	Mild	N	0	Probable	Recovered
		Antibody test positive	Severe	N	28	Probable	Recovered
	60	Incorrect dose administered	Mild	N	0	Probable	Recovered
	16	Antibody test positive	Mild	Y	16	Possible	Recovered
	14	Antibody test positive	Mild	Y	16	Possible	Recovered
	8	Injection site pain	Mild	N	2	Possible	Recovered
		Fibrin D dimer increased	Mild	N	14	Probable	Recovered

SOC: System Organ Class PT: Preferred Term Not recov.: Not recovered

* Age at baseline

** Days since the preceding dose of rFXIII

*** Outcome as recorded at the end-of-trial visit approximately two months after onset of the event

**** Worsening of mild neutropenia initially diagnosed before first trial drug administration.

Source: Original BLA 125398; Clinical Study Report module 5.3.4.3, p.60 Table 12-3

There were no thrombotic adverse events.

Potential Risk for Immunogenicity. There were 4 subjects [(b) (6)] who demonstrated antibody reactivity to rFXIII in scheduled pre-dosing antibody tests. These antibody responses were observed after 2 or 3 product doses. Three of these antibody-forming subjects [(b) (6)] were discontinued from further treatment, but were followed for safety for the duration of the study. None of these subjects demonstrated clinically-apparent FXIII inhibitors, and the applicant reports none had evidence of “neutralizing” antibodies in an *in vitro* assay [see [section 4.2](#) for antibody detection procedures, and [section 8.4.8](#) for clinical details on the four antibody-forming subjects]. This review questions whether the assays used to classify an anti-FXIII antibody as being a “neutralizing antibody” have been validated for clinical relevance.

Risk Management Plan. The applicant identified the following as potential risks to be addressed:

1. non-neutralizing antibodies,
2. neutralizing antibodies,
3. allergic reactions,
4. thromboembolic events, and
5. lack of efficacy

To address these risks, the applicant proposes to continue routine post-market surveillance and to use “structured follow up forms” to supply additional details on passively reported events. Labeling is also used to address these identified risks. [See [section 11.2](#) for more information on the Risk Management Plan.]

Recommendations.

1. Recommend that all labeling use mass units to describe dosing, and not activity units. The submission incorrectly uses the international standard for plasma Factor XIII to assign activity units to a product that is not plasma Factor XIII. This recommendation should be discussed before the Blood Products Advisory Committee.
2. Ask the sponsor to re-evaluate the dataset used to derive the historical control annual bleed rate. Subjects with outlying bleed rates (e.g., 11 and 12 bleeds per year) should be eliminated from the dataset. The statistical analysis should be repeated using the new historical control rate.
3. Ask the sponsor to conduct a pharmacokinetics study in FXIII congenitally-deficient subjects who have been exposed to NovoThirteen through at least two monthly administrations for routine prophylaxis. The purpose is to further investigate potential immunogenicity that may have been missed in the clinical studies to date.
4. **Postmarket Requirement (PMR).** Ask the sponsor to conduct a clinical trial as a Post-Market Requirement (PMR) to evaluate the risk for forming neutralizing antibodies to Factor XIII after re-treatment with NovoThirteen after the observance of treatment-emergent non-neutralizing antibodies to NovoThirteen. Four subjects demonstrated non-neutralizing antibodies to NovoThirteen in Study F13CD-1725, however only one of these subject continued on-study. Since all patients who develop such antibodies post-licensure will be unaware of this event, and will continue to be treated with NovoThirteen, the potential risk associated with this event remains un-evaluated at the present time.

Letter-ready Comments:

1. The immunogenicity of NovoThirteen® and the potential clinical consequences of an antibody response to the product have not been fully characterized by the clinical studies conducted to date. Three of the four subjects who scored positive for “neutralizing antibodies” in your in-house assays were discontinued from dosing and followed only for safety. The exclusion of these antibody responders from further exposure to NovoThirteen® means that there is no information on outcomes for patients who will be exposed to NovoThirteen® post-licensure, and who will form “neutralizing antibodies” to NovoThirteen®, and who will continue to be exposed to NovoThirteen® because their antibody status will not be known to them or their physicians.

Therefore, there will be a post-marketing requirement for a safety study that can provide additional safety information for this patient group.

2. There is no formal repeat-dose pharmacokinetics study in the indicated population. This is now of concern due to the observation of antibody formation

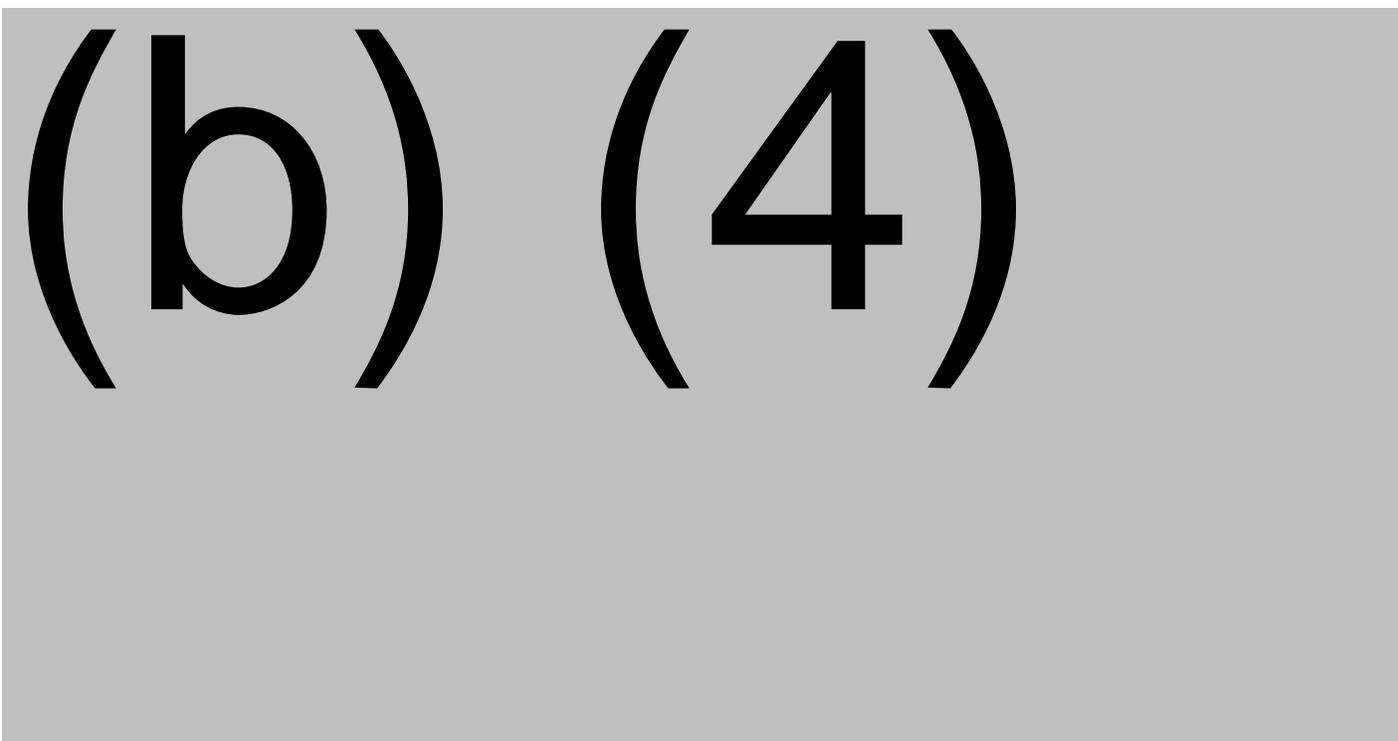
to the study agent in approximately 4 (10%) of the enrolled subjects, and the lack of information on the clinical effects of antibody formation due to the removal of most of these subjects from further exposure to the product.

Many of the other subjects had 1-hour post-dose FXIII activity levels that were less than the targeted level of 1 IU mL, and yet there are no data to show what levels they maintain over the month until their following study visit.

To address this safety concern, please submit a final study report for a PK study conducted in FXIII congenitally-deficient subjects who have been exposed to at least two monthly exposures to NovoThirteen® through a routine prophylaxis dose schedule.

3. The final report titled “NN0665-979-B Anti-Factor XIII antibodies Determination of the Isotype and Cross reactivity of anti-FXIII Antibodies in Human plasma (EDTA) Using (b) (4) is important because it contains information that appears to show that NovoThirteen® behaves differently from plasma-derived Factor XIII (Fibrogammin P) when each is used as a competitive inhibitor in an (b) (4) assay in which the capture agent is NovoThirteen® and the positive control detection agent is antiserum positive for anti-Factor XIII antibodies that was collected during the (b) (4) repeat dose study NN205255.

The following table is taken from the study report for NN06650979-B:



There is a difference between plasma-derived Factor XIII and NovoThirteen® in the extent to which each can compete for the anti-rFXIII A₂ positive control

antibodies. In Table 4, the blue background highlights the results for inhibition of the high dose positive control by two NovoThirteen® products. These products differ only in the site where they were manufactured. The yellow background highlights the results for inhibition of the high dose positive control by Fibrogammin P.

It can be seen that the recombinant Factor XIII's inhibit in the range of 77-82%, whereas Fibrogammin P inhibits only in the range of 52-57%.

The report conjectures that this difference is due to antigen epitope blocking by the B-subunit of Factor XIII, which is present in Fibrogammin P but not in NovoThirteen®.

Another possibility is that NovoThirteen® contains antigenic determinants that are not present in Fibrogammin P. Please comment.

Please submit a final study report for a nonclinical study that can explain the apparent differences in antigenic structure between NovoThirteen® and Fibrogammin P.

4. The following items concern the assays used to measure anti-rFXIII_{A2} activity:
 - a. The outcomes of the assay procedures that are used to classify antibodies as “antigen-specific” (AS) or “not antigen-specific” (NAS) are apparently dependent on the titer of the antibody being studied. There are several subjects who are classified as having “antigen-specific” antibodies at certain study visits, and who are then classified as having “not antigen-specific” antibodies at study visits immediately preceding or following.

Due to this uncertainty about the clinical meaning of the observation of antibodies to FXIII which do not interfere with the Berichrom assay, but which may interfere with some FXIII functions (pharmacokinetics, fibrin cross-linking), we think it is not appropriate to describe the anti-FXIII antibodies observed in study F13CD-1725 as “non-neutralizing”. Please remove categorizations of antibody formation to the product based upon “neutralization” from the product label, or submit a final report that clinically validates the use of the Berichrom assay for the detection of neutralizing antibodies to the product.

5. On page 53 of 705 of the F13CD-1725 study report, in section 11.3.1.2 Clot Solubility, you state as follows:

The fact that there are 46 clot lysis observations for FXIII activity levels >0.10 IU/mL reflects that the Berichrom® assay for quantifying FXIII activity levels is prone to stochastic variations (especially at low activity levels).

We note that another possible explanation for this finding may be that subjects may have antibodies to the product that interfere with the clot stabilization process, but not with the chromogenic Berichrom® assay, which measures

(b) (4)

for the measurement of circulating Factor XIII.

6. Sibling subjects (b) (6), both of whom formed anti-rFXIII_{A2} antibodies very soon after initial exposure to NovoThirteen®, were removed from treatment but were monitored for safety for the full study period. The 1-hour post-dose FXIII activity levels for each of these subjects remained low for the full study period, and the A₂B₂ heterotetramer levels (i.e. the FXIII antigenic levels) also remained low at the 1-hour post-dose time point for the full study period.

Please submit the routine prophylaxis dose schedule for each of these subjects for the full study period. Please analyze the 1-hour post-dose FXIII activity data to determine whether anti-FXIII antibodies may have decreased the expected level of FXIII activity, based upon what is known about the pharmacokinetics of the FXIII-containing product they received for routine prophylaxis.

7. The following comments pertain to the adverse events database:
- a. Subjects (b) (6) experienced the adverse events pollakiuria, dysuria, or polyuria. Please submit additional information about these adverse events, including the time relationship to previous dose of the product, the visit number, and the reasons these adverse events were judged to be unlikely related to product administration.

- b. The submitted report for study F13CD-1725 states there were 231 treatment emergent adverse events (TEAEs) observed in 32 subjects. Our analysis of the submitted data database 'ADAE' reveals 232 adverse events in 32 subjects, with the discrepancy falling in the category "**Infections and infestations.**" Please identify the subjects and adverse events that explain this discrepancy and justify any adjustments made to the database.
 - c. The submitted report for study F13CD-3720 states there were 98 treatment emergent adverse events (TEAEs) observed in 20 subjects. Our analysis of the submitted data database 'ADAE' reveals 99 adverse events in 20 subjects, with the discrepancy falling in the category "**Injury, poisoning and procedural complications.**" Please identify the subjects and adverse events that explain this discrepancy and justify any adjustments made to the database.
8. Subject (b) (6) an 8 year old child, was withdrawn after visit 6 for "worsening leukopenia and worsening neutropenia." This subject had repeat-reactive, antigen non-specific, antibodies at visit 6, none of the 1-hour post-dose FXIII activity levels exceeded 0.5 IU/ml (i.e. less than the targeted level of 1.0 IU/mL), and for the final two visits the pre-to-post-dose changes in B subunit were small (in the bottom 10%). These results are characteristic of anti-FXIII antibody formation.

Please submit a narrative describing the adverse events that caused the withdrawal of subject (b) (6) Please submit an update of the medical status of subject (b) (6) including data on the current anti-FXIII antibody status.

9. Please submit a narrative describing the adverse event "pain in extremity," judged possibly related to the study agent and categorized as "not recovered", for subject (b) (6) Please explain how the event is thought to be possibly related to the study agent.
10. Listing 7, titled "After initiation of treatment – On-demand Treatment" (page 26 of 26 in the selected listings for the report of Trial ID: F13CD-QUEST), lists the reported number of bleeds per year requiring on-demand treatment. This listing provides the data for the historical control group that is used to demonstrate the efficacy of NovoThirteen[®] for the routine prophylaxis indication.

Please remove subject (b) (6) (11 bleeds per year reported) and subject (b) (6) (12 bleeds per year reported) from the database because their reported bleed rates are outliers. Please re-calculate the statistical analysis of study F13CD-1725 and submit the results.

We acknowledge your response to the previous FDA request (September 22, 2011) to re-analyze the data after removing these two outliers from the control group, in which you state these two subjects may represent the natural variation in

bleed rates for this rare disorder. However, the use of a historical control group can introduce bias into the analysis due to imbalances in baseline characteristics; therefore, a more conservative approach is needed.

11. In addition to the planned analysis for efficacy, please submit separate analyses for the pediatric and adult age groups.

12. Please submit a dot-plot of the 1-hour post-dose data for study F13CD-1725 in database ADPROF for the A₂B₂ heterotetramer levels (i.e. antigenic FXIII levels) plotted on the ordinate versus the FXIII activity levels plotted on abscissa. Please analyze the data to evaluate the correlation coefficients for the regions FXIII activity < 1 IU/mL and FXIII activity > 1 IU/mL, and describe the extent to which the results are to be expected based upon the study procedures and the analytical procedures that were employed.

2. Clinical and Regulatory Background

The regulatory approach to rFXIII_{A2} (NovoThirteen[®]) was guided by a recognition of the need for safe and effective products for replacement therapy in a very rare disease. At the same time, the regulatory approach was mindful of the fact that this product is not Factor XIII, and therefore, it may have associated risks that can only be evaluated from observations in clinical studies.

2.1 Disease or Health-Related Condition(s) Studied

Information on the clinical presentation of congenital Factor XIII deficiency is not abundantly available due to the scarcity of the condition. Many publications are based on anecdotal evidence, and event rates have low precision. The following table gives the results of one study that examined bleeding events in Factor XIII-deficient patients:

Table 1 Bleeding Sites in FXIII Deficiency

Bleeding Sites	Percentage of Patients Affected (%)
Umbilical bleeding	80
Superficial bruising	60
Subcutaneous hematoma	55
Mouth and gums	30
Intracranial hemorrhage	30
Muscles	27
Lacerations	26
Joints	24
After surgery	17
Peritoneal	14
Epistaxis	10
Genital	9
Renal	8
Peripheral nerves	6
Eyes-gastrointestinal-spleen	3
Ears	2
Pleural	1

Source: Adapted from - *Sem. Thromb. Hemostas.* 35(4): 426- 438 (2009)
“Factor XIII Deficiency” Mehran Karimi, M.D., Zsuzsanna Bereczky, M.D., Ph.D.,
Nader Cohan, M.Sc., and La’ szlo’ Muszbek, M.D., Ph.D.

Annualized bleeding event rate information is not readily available in the literature, perhaps because, although such information is of interest to researchers and drug regulators, it is not needed information for physicians who treat this rare disorder.

A recent publication reports data from a retrospective chart review to capture bleeding event rate information as part of an effort to evaluate the prophylactic efficacy and long-term safety of a plasma-derived Factor XIII product, Fibrogammin® P. These data are shown in the following table:

Table 1. Bleeds before vs. during Fibrogammin® P therapy

		Pre-Fibrogammin® P therapy				Fibrogammin® P therapy			
Patient	Age* (years, unless noted)	Observation period (months)	No. of bleeds	Type of bleed	Acute treatment	Observation period, months; (no. of infusions)	No. of bleeds	Type of bleed	Dose (units kg ⁻¹)
(b) (6)	5	24	2	Haematomas, right thigh and rib cage	None	12 (12)	0		27
	10 months	9	2	Umbilical cord; extensive bruising	FFP, vit K	25 (26)	1	Head trauma and bruising	29.7–44.9
	17 months	6	3	Forehead bruise; frenulum bleed; forehead haematoma	FFP	26 (26)	2	Soft tissue bleed from trauma to foot; extracranial head	18.3–43.1
	9	24	3	Lower lip; ankle; forehead haematoma	FFP	13 (12)	0		19.9–29.7
	19	24	5	Various haematoma; forehead bruise	FFP	9.5 (11)	0		18.9
	17	24	0	None	None	9.5 (12)	0		24.3
	14	24	8	Intracranial; mouth; forehead; gums; thigh	FFP	19 (11)	0		15.6
Mean no. bleeds per year			2.5 per year	Mean no. bleeds per year			0.2 per year [†]		

FFP, fresh-frozen plasma

*Age at onset of Fibrogammin® P therapy

[†]P = 0.01 vs. pretherapy
Source: Lusher, J. *et al.*, *Haemophilia* 1-6 (2009)

Inhibitors against Factor XIII in congenitally FXIII-deficient patients.

It is rare for congenitally FXIII-deficient patients to form inhibiting antibodies against Factor XIII, as stated in the following paragraphs from three recent reviews of Factor XIII deficiency:

- *British Journal of Haematology* (107):468-484 (1999)
 - In inherited FXIII deficiency, inhibitors such as antibodies to injected FXIII arise very rarely. Only two cases have been published and no information on management of these cases is available (Lorand et al, 1969; Henriksson et al, 1983). Rarely FXIII inhibitors arise de novo, in the course of other diseases, and often in relation to chronic therapy with a variety of drugs (Lorand et al, 1980; Board et al, 1993). Bleeding in these cases may be severe and difficult to treat. Several cases have died of cerebral haemorrhage (Lorand et al, 1980). Most of the inhibitors described are antibodies. Treatments attempted include immunosuppression with steroids and cyclophosphamide, administration of large doses of FXIII, and plasma immunoadsorption. In a recently reported case an inhibitor appeared in a patient without any obvious chronic disease (Tosetto et al, 1995). She responded well to cyclophosphamide combined with large doses of FXIII.
- *Semin Thromb Hemost* (35):426–438 (2009)
 - Inhibitor formation against FXIII during the course of replacement therapy is exceptionally rare. To test this possibility, a mixing study (FXIII activity determination on the mixture of patient and normal plasma) would need to be performed. In the presence of neutralizing antibody, FXIII present in normal plasma will be inhibited.
- *Haemophilia* (14):1190–1200 (2008),
 - Although there is a lifelong risk of bleeding with FXIII deficiency, the prognosis is excellent because of the good response to treatment with FFP, cryoprecipitate or plasma-derived FXIII concentrate. Because the half-life of FXIII is long, prophylaxis is easily accomplished for those patients with the worst bleeding history and the incidence of inhibitor development is extremely low.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

The only licensed product for this indication is Factor XIII Concentrate (Human) (Corifact®). Cryoprecipitate is commonly used to provide source of Factor XIII for replacement therapy.

Of relevance to this review, none of the 187 subjects treated with Corifact during the investigational phase developed anti-FXIII inhibitors, however one subject in the ongoing phase 4 study B171023_2002 experienced an adverse event consistent with formation of an inhibitor (see Summary Basis for Regulatory Action, STN 125385).

2.3 Safety and Efficacy of Pharmacologically Related Products

The following information is from the FDA clinical review memo of Daniela J. Vanco, M.D., for the licensure of Corifact®:

- CSL Behring GmbH (CSLB), Applicant, submitted the BLA for Factor XIII Concentrate (Human) under the Accelerated Approval regulation [21 CFR 314.510] using Factor (F) XIII activity trough levels as the surrogate endpoint.
 - a post-marketing study to correlate the achieved plasma FXIII trough levels to clinical benefit is currently ongoing.
- Corifact™, is indicated for routine prophylactic treatment of congenital FXIII deficiency.
- Clinical efficacy is to be determined in a post-marketing Phase 4 Study, which is designed to show the correlation of the trough FXIII levels (a surrogate marker) and the clinical outcomes during treatment of bleeding episodes in patients with congenital FXIII deficiency.
- Corifact is a lyophilized concentrate for reconstitution, administered intravenously at the initial dose of 40 International Units (IU)/kg body weight.
 - Subsequent Dosing should be guided by the most recent trough FXIII activity level, with dosing every 28 days (4 weeks) to maintain a trough FXIII activity level of approximately 5% to 20%.
 - Recommended dosing adjustments of ± 5 IU/kg should be based on trough FXIII activity levels of $<5\%$ or $>20\%$ as outlined in Table 1, and the patient's clinical condition. Dosing may need to be adjusted following a bleeding event.

FXIII Activity Trough	Dosage Change
One trough level of $<5\%$	Increase by 5
Trough level of 5% to 20%	No change
Two trough levels of $>20\%$	Decrease by 5
One trough level of $>25\%$	Decrease by 5

The injection rate should not exceed 4ml per minute.

- Twelve studies contributing to the overall clinical development of Corifact, included 187 subjects, 90 of whom were subjects < 16 years old. In the pivotal study, the efficacy population consisted of 13 patients and safety population of 14 patients, of whom 5 were subjects < 16 years old.
 - Total of 3,930 doses of Factor XIII Concentrate (Human) have been administered in the 12 clinical trials included in this BLA application. Of the 3930 doses of Factor XIII Concentrate (Human), 3,590 doses were administered to subjects with rare congenital Factor XIII deficiency.
- There were no deaths, life-threatening events or adverse events that led to study discontinuation in the pivotal study to support this BLA application.
 - Eight subjects in the study experienced treatment-emergent adverse events (TEAE) of mild to moderate severity (5 subjects experienced infections, injury, bruising and contusion, ecchymosis, borderline diabetes), three subjects within 24 hours, three subjects within 72 hours of infusion.
 - No episodes of thrombo-embolism or viral transmission were identified during the study.
 - The two occurrences of laboratory increases (thrombin-antithrombin III complex increased and prothrombin increased and fibrin D-dimer increased) were not associated with any clinical signs of thrombo-embolism, and were possibly related.
 - One subject experienced a mild rash on Day 65 that was considered unrelated to study product and was ongoing.
- In post-marketing reporting, an SAE consistent with a neutralizing inhibitor to Factor XIII was reported in a 26-year old subject with congenital FXIII deficiency.
 - The patient's FXIII levels returned to baseline after plasmapheresis.
 - The patient was re-exposed to Corifact™ and has not reported any breakthrough bleeding.
- In a study of [redacted], consisting of 33 subjects, one subject experienced a myocardial infarction (MI) .
 - This subject was a 74-year old male with a history of coronary heart disease and suffered acute myocardial infarction one day after the last study drug infusion.
 - The subject was not Factor XIII deficient and received five times the dose given for congenital deficiency patients.
- In the post-marketing safety surveillance, an MI was reported seven days after administration of Fibrogammin P (trade name of Corifact™ in EU) in a congenital deficient patient.
 - The causality was assessed as possible.
- Two other cases of thrombi-embolic events were reported in patients with no known FXIII deficiency. The causality was assessed as possible
- The review of the clinical data does not raise any safety concerns with regard to thrombogenicity and immunogenicity.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

NovoThirteen® has not been approved for marketing in any country.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Regulatory Chronology.

(b) (4)	
September 2002	IND 10674 for rFXIII A subunit submitted by (b) (4) (re-established as an independent company in 2000)
May 2003	Orphan drug designation for congenital FXIII-deficiency Therefore: PREA does not apply
August 2005	IND 10674 sponsorship transferred to Novo Nordisk, Inc.
December 2005	IND 10674 Amendment 25 contained a Special Protocol Assessment (SPA) request for phase 3 study for Routine Prophylaxis in FXIII congenitally-deficient subjects; February 2, 2006, FDA letter responded to this request and placed the study on clinical hold for design issues [<i>see section 5.2</i>]
August 2006	IND 10674 clinical hold continued because Amendment 26 final study report for (b) (4) repeat-dose study showed anti-FXIII autoantibody formation to be assessed by sponsor [<i>see section 4.3</i>]
October 2007	Clinical hold removed after toxicology review
May 2010	IND 10674 placed on partial hold (sponsor-requested) to impose review timelines for review of manufacturing change ((b) (4) produced material to Novo Nordisk production)
Nov. 19, 2010	Pre-BLA Meeting for STN 125398

2.6 Other Relevant Background Information

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was well-organized and of good quality, however there were important omissions of original data. For example, the original data for the analysis of anti-FXIII antibodies was not submitted, and had to be requested. Also, the information on

individual subjects was sparse, including the 4 subjects who formed antibodies to rFXIII_{A2}.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The clinical studies appear to have conformed to Good Clinical Practice guidelines.

3.3 Financial Disclosures

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

The following CMC issues are important concerns for the safe and effective clinical use of this product:

1. Contamination of the FXIII_{A2} product with the activated coagulation factor form of the product may be a source of adverse reactions (thrombosis). This would represent an exaggerated effect of the expected pharmacologic action (clot stabilization).
2. The product should be labeled and dosed in mass units, and not in FXIII activity units. Although this FXIII_{A2} product has shown pharmacokinetic and pharmacodynamic properties that are similar to those reported for plasma-derived Factor XIII, other tests (e.g., (b) (4) study) has shown differences between this product and plasma-derived Factor XIII. It would be misleading to represent this product as being the same or similar to for plasma-derived Factor XIII, and it would set a precedent for future FXIII products that may be even more different from plasma-derived Factor XIII.

4.1 Chemistry, Manufacturing, and Controls

4.2 Assay Validation

Antibodies against Factor XIII

Results from the preclinical study [NN205255](#), titled “Recombinant FXIII: 27 Week Intermittent Intravenous Administration Toxicity Study in the Monkey Followed by an 8 Week Reversibility Period” raised concerns about the potential immunogenicity of rFXIII (NovoThirteen[®]). Therefore, subjects were monitored for anti-FXIII antibodies according to a 3-tier system, as follows:

1. **Tier 1:** anti-rFXIII (b) (4) at screening, Visit 1 (baseline), and each visit through Visit 16
 - a. Tier 1 determines the reactivity of antibodies against rFXIII and is set to generate (b) (4) false reactive samples from a healthy population.
 - b. The anti-rFXIII (b) (4) used a (b) (4) anti-human IgG + IgM + IgA reagent
 - c. The cut-off for positives was based on the mean (b) (4) standard deviations of results from sera from (b) (4) healthy persons
 - d. Output:

- LTR – Lower Than Reportable
 - R – Reactive
2. **Tier 2:** Specificity (cross-reactivity) assay
(b) (4)
- e. Output:
- LTR – Lower than reportable (results of Tier 1 could not be verified)
 - RR – Repeat Reactive
 - NAS – Not Antigen Specific
 - AS – Antigen Specific
3. **Tier 3:** Titration of Antibody Positive Samples
- a. Samples considered reactive were re-analysed following (b) (4) with assay buffer
- b. The titer measurement was based on the log10 of the dilution necessary to cross the cut-point which was specific for each matrix

As Novo Nordisk states in STN125398.02, the response to the August 2, 2011, FDA request for information (page 4):

“Tier 3 estimates the titre of AS samples. If antibody levels are close to assay detection limit, i.e. the plate-specific cut-point (PSCP), a positive titer is not always obtained (Titer^{(b) (4)}). A sample is considered positive if the reactivity of the sample can be specifically displaced by rFXIII (Tier 2, antigen-specific). In the presence of rFXIII binding antibodies ((b) (4) RR-AS), it is important to determine if the antibodies affect the pharmacodynamics and pharmacokinetics of rFXIII and thus the expected prophylaxis of bleeding by rFXIII. Thus, a functional inhibitory assay based on Berichrom® is performed to assess the neutralizing activity of the (b) (4) positive sample.”

Reviewer’s Comment:

It is import to recognize that the definition of “antigen specific” (AS) is dependent on the titer of the antibody because it is dependent upon the demonstration of a percent reduction in a positive signal. If the titer of an “antigen specific” (AS) antibody sinks below the limit of the ability of the test to measure the defining

percent reduction level, the assay protocol requires the result to be classified as non-antigen specific (NAS). This explains the paradoxical shifting between AS and NAS responses that can be seen in some of the outcome classifications of study F13CD-1725 presented in Appendix 2.

Neutralizing Antibodies against Factor XIII

Samples that were judged to be antigen-specific (AS) were then tested for their ability to neutralize FXIII activity in the Berichrom® assay.

- The positive controls for the neutralization assay were *not the* (b) (4) *anti-rFXIII antibodies used in the antibody detection assay*, rather the positive controls were dilutions of a commercially obtained (b) (4) *anti-human Factor XIII antibody* preparation.
- The validation of the neutralizing antibody assay is described in the submitted report titled, “Validation of NN1841 neutralising antibody assay for human FXIII deficient plasma.”
 - Validation is based on the ability to detect a reduction of FXIII activity in plasma sample that falls below (b) (4) standard deviations of the average of the FXIII activities of plasma samples obtained from (b) (4) FXIII-deficient patients that were spiked with (b) (4) NovoThirteen.
 - By setting this cutpoint, the applicant claims the neutralization assay allows a (b) (4) *false positive rate*.
- The measurement of FXIII neutralization activity is described in the submitted report titled “Analysis of anti-FXIII inhibitors in antibody screening positive samples from Trial ID: F13CD-1725.”
 - The following is from the study report:

The assay was based on a photometric assay developed by Dada Behring for determination of FXIII clotting activity (Berichrom® FXIII, Dada Behring, Marburg, Germany).

(b) (4)



1 page determined to be non-releasable: (b)(4)

(b) (4)

Acceptance criteria

(b) (4)

The FXIII neutralization assay results for the 4 subjects who formed antibodies to rFXIII are given in the following Table 2 taken from the submitted report:

Table 2 Results

Run	Sample	Sample Id	Activity (%)	Activity (U/ml)	Avg Activity (U/ml)	Residual Activity (%)	Neutralisation (%)
2	5	(b) (6)	58.70	0.59	0.59	114	
2	5	(b) (6)	58.40	0.58			
2	6	(b) (6)	51.10	0.51	0.52	100	
2	6	(b) (6)	49.10	0.49			
2	6	(b) (6)	52.80	0.53			
2	6	(b) (6)	53.00	0.53			
2	7	(b) (6)	59.50	0.60	0.59	115	-15
2	7	(b) (6)	59.10	0.59			
2	8	(b) (6)	52.80	0.53	0.52	102	-2
2	8	(b) (6)	52.00	0.52			
2	9	(b) (6)	54.40	0.54	0.55	111	
2	9	(b) (6)	55.30	0.55			
2	10	(b) (6)	50.80	0.51	0.50	100	

		(b) (6)					
2	10		50.60	0.51			
2	10		48.50	0.49			
2	10		48.30	0.48			
2	11		56.90	0.57	0.58	117	-17
2	11		59.30	0.59			
2	12		50.80	0.51	0.52	104	-4
2	12		52.70	0.53			
3	5		58.00	0.58	0.58	112	
3	5		58.50	0.59			
3	6		52.50	0.53	0.52	100	
3	6		51.40	0.51			
3	7		60.70	0.61	0.61	118	-18
3	7		62.20	0.62			
3	8		56.90	0.57	0.56	109	-9
3	8		55.90	0.56			
3	9		56.40	0.56	0.56	107	
3	9		56.10	0.56			
3	10		52.80	0.53	0.53	100	
3	10		52.60	0.53			
3	11	59.00	0.59	0.58	111	-11	
3	11	57.60	0.58				
3	12	57.70	0.58	0.57	109	-9	
3	12	56.80	0.57				
4	4	72.20	0.72	0.72			
4	4	72.00	0.72				
4	5	69.30	0.69	0.69	102		

		(b) (6)					
4	5		68.90	0.69			

The applicant concludes that no sample from the 4 subjects who formed antibodies against rFXIII demonstrated FXIII neutralizing activity in this assay.

Reviewer's Comment. It is not clear how this *in vitro* FXIII neutralization assay, which uses the Berichrom assay for detection, would correspond to *in vivo* neutralization of FXIII activity. *In vivo* FXIII neutralization would depend on many factors, such as alteration of pharmacokinetic parameters, which would not be captured by the *in vitro* assay. In the (b) (4) monkey repeat dose study NN1841 (see section 4.3), there was clear evidence of anti-FXIII autoantibody formation as seen by the depressed plasma FXIII activity levels compared to the baseline levels. Unfortunately, the sponsor did not use (b) (4) anti-FXIII antibody positive serum for the positive control in the FXIII neutralization studies, but instead used (b) (4) anti-FXIII serum. Therefore, it is not known to what extent the neutralization assay would detect the (b) (4) antibodies that depressed the FXIII plasma levels.

4.3 Nonclinical Pharmacology/Toxicology

The repeat-dose study in (b) (4) monkeys is potentially informative for immunogenicity safety, and is discussed here in that regard. Other nonclinical toxicology information is contained in the toxicology review of La'Nissa Brown, Ph.D.

The information on the repeat-dose (b) (4) monkey study NN205255 is contained in the report titled "NN1841 recombinant FXIII: 27 Week Intermittent Intravenous Administration Toxicity Study in the Monkey Followed by an 8 Week Reversibility Period."

Study design for NN205255:

- 26 male and 26 female, (b) (4) monkeys
- 5 treatment groups plus one vehicle control group, each group comprising 3-5 male and female animals
- Animals received every 2 weeks for 13 or 27 weeks (depending on group) intravenous administration of rFXIII of
 - 0 mg/kg (Group 1) 5M + 5F (including 2+2 for recovery),
 - 1 mg/kg (Group 2) 3M + 3F,
 - 3 mg/kg (Group 3) 3M + 3F or
 - 10 mg/kg (Group 4-6) each group 5M + 5F
- The duration of treatment was
 - 27 weeks (Group 1-5) and
 - 13 weeks (Group 6), followed by a treatment-free period of 8 weeks in 2 male and 2 female animals of Groups 1, 4, 5 and 6.

- Dosing was originally anticipated to continue for 39 weeks in Group 1-4. However, due to the apparent effect of cross-reacting neutralising antibodies resulting in decrease in pre-dose FXIII activity in all rFXIII treatment groups, the dosing period was shortened to 27 weeks.

The following graphs show the Factor XIII activity levels (as measured by a modified Berichrom[®] assay) and the anti-FXIII antibody activities as measured by (b) (4) :

It is not unusual to observe autoantibody formation in nonclinical studies when primates are dosed with human proteins. This has been observed with some recombinant Factor VIII products, apparently without subsequent clinical consequences. However, it is well-known that clinical exposure to bovine thrombin products that are contaminated with bovine factor V can cause autoantibody formation against endogenous human Factor V, with serious clinical consequences.

There were four subjects in study F13CD-1725 who formed antibodies against rFXIII_{A2}, three of whom were then discontinued from further exposure to rFXIII_{A2}. Therefore, it is not known if there are clinical consequences to antibody formation to rFXIII_{A2} after clinical exposure.

rFXIII_{A2} (NovoThirteen[®]) is Antigenically Distinct from Fibrogammin P in Competitive Inhibition Assays

The final report titled “NN0665-979-B Anti-Factor XIII antibodies Determination of the Isotype and Cross reactivity of anti-FXIII Antibodies in Human plasma (EDTA) Using (b) (4) contains additional data on the characterization of the immune response to rFXIII_{A2}.

The most informative assay was a (b) (4) assay. In this assay, rFXIII_{A2} was the (b) (4) for (b) (4) serum samples from study NN1841, and Factor XIII (0.76 IU/mL) was included in the incubation buffer to evaluate the extent of (b) (4) of sample serum (b) (4) to the (b) (4).

This format is similar to the Tier 2 antigen specificity assay that was used to characterize repeat reactive (RR) samples from the phase 3 study F13CD-1725. Like the Tier 2 assay, this assay used positive controls for antigen binding that were taken from (b) (4) monkey 47 in group 5 (above). Like the Tier 2 assay, the negative control competitive inhibitor was rFVIIa (Novoseven[®]). Unlike the Tier 2 assay, there were three (not one, as in the Tier 2 assay) positive control competitive inhibitors, as follows:

- rFXIII 103.1841.05.1 (10µg/mL; 0.76 IU/mL)
- rFXIII XR40371 (0.76 IU/mL)
- Fibrogammin P (0.76 U/mL)

Novo Nordisk states product rFXIII 103.1841.05.1 “was created using the same process as the FXIII given to the subjects” (i.e. manufactured by (b) (4) and that rFXIII XR40371 was manufactured by a different company (presumably by Novo Nordisk). Fibrogammin P (CSL Behring) is plasma-derived Factor XIII, licensed in Europe (the U.S.-licensed version of Fibrogammin P is called Corifact[®]).

The results of the characterization of control results in this (b) (4) assay are presented in Table 4 of the study report, as shown here:

(b) (4)

Novo Nordisk summarizes these results as follows:

Both the FXIII reagents exhibited higher % reduction than the Fibrogammin, which was to be expected as Fibrogammin represent FXIII heterotetramer (A₂B₂) and rFXIII is equal to the homodimer, FXIII-A₂. It is believed a part of the epitopes present on the homodimer will be shielded in the heterotetramer complex.

Reviewer's Comment:

There is a very clear difference between Fibrogammin P (plasma-derived Factor XIII) and recombinant Factor XIII_{A₂} (NovoThirteen[®]) in the extent to which each can compete for the anti-rFXIII A₂ antibodies that are present in the serum of the group 4 (b) (4) monkey 47. In Table 4, the blue background highlights the results for inhibition of the high dose positive control by the two recombinant Factor XIII products. These products differ only in the site where they were manufactured. The yellow background highlights the results for inhibition of the high dose positive control by Fibrogammin P. It can be seen that the recombinant Factor XIII's inhibit in the range of 77-82%, whereas Fibrogammin P inhibits only in the range of 52-57%.

Novo Nordisk's explanation -- that this may be due to shielding of epitopes on the plasma-derived Factor XIII in Fibrogammin P by the B-subunit -- is a formal

possibility; however, it is also possible that recombinant Factor XIII_{A2} (expressed in yeast) contains epitopes that are not present on plasma-derived Factor XIII even if the B-subunit were not present. Novo Nordisk has not submitted results from experiments that can help decide between these possibilities, which may have different clinical consequences.

Novo Nordisk Investigated a Potential Renal Toxicity in the Monkey Studies.

The submission contains a report titled “Review of Histopathological Kidney Findings from Two Monkey Studies Conducted at (b) (4) and One Conducted at (b) (4) on rFXIII,” that can be summarized as follows (adapted from the report):

- Study (b) (4) **1266-175**, an early dose range finding study
 - one monkey given three intravenous doses at two week intervals of 12.5 mg/kg of rFXIII , then sacrificed terminally on Day 30
 - observed changes to the morphology of the renal glomeruli, particularly in the thickness of the mesangial matrix, which was termed “mild glomerulopathy” and reported as being **related to treatment**
- Study (b) (4) **1394-175** conducted at the same laboratory ((b) (4))
 - daily intravenous injections for 14 days at doses up to 6 mg/kg
 - observed similar changes in controls and treated monkeys which were reported as **incidental or spontaneous**
- Study **0665-579** (a.k.a. NN1841), conducted at (b) (4)
 - intravenous doses of up to 10mg/kg at two week intervals for 13 or 27 weeks
 - **no treatment-related changes in the renal glomeruli were noted**
- An overview of the three studies was conducted by an independent consultant pathologist (b) (4).
 - High resolution scanned images of the kidneys from the two studies conducted at (b) (4) and the kidney slides from the (b) (4) study were examined
 - It was seen that the glomeruli in all the treated and control monkeys from the three studies varied greatly in their appearance, particularly in the thickness of the mesangial matrix.
 - Although the author considered this represented a natural variation related to the functional state of each glomerulus, the thickening of the mesangial matrix was graded for all monkeys.
 - **The overview indicated that there was no treatment related effect on the glomeruli.**
 - All the glomerular changes seen were considered part of the normal spectrum of changes seen as the spontaneous background in (b) (4) monkeys.
- The only renal lesion seen in the three studies which was associated with treatment was the **wedges of coagulative necrosis in the kidney** seen in a monkey which died five days after a single dose of 10mg/kg in the (b) (4) study.

- It is considered that the renal lesion is of ischemic origin probably caused by thrombus formation and related to an exaggerated pharmacological response to rFXIII in the monkey.

4.4 Clinical Pharmacology

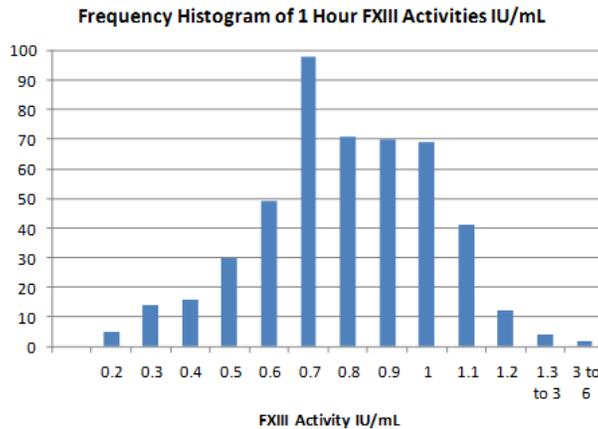
4.4.1 Mechanism of Action

NovoThirteen[®] is recombinant Factor XIII A subunit homodimer (rFXIII_A₂) expressed in yeast. It is not identical to human plasma-derived Factor XIII in its antigenic properties; however, after intravenous administration it combines with free plasma Factor XIII B subunits to form a heterotetrameric structure (A₂B₂) that has pharmacokinetic and pharmacodynamic properties that are very similar to native human Factor XIII. The mechanism of action is by replacement of plasma Factor XIII activity to levels above the 5% of normal Factor XIII level to avoid spontaneous bleeding in congenitally Factor XIII deficient patients.

4.4.2 Human Pharmacodynamics (PD)

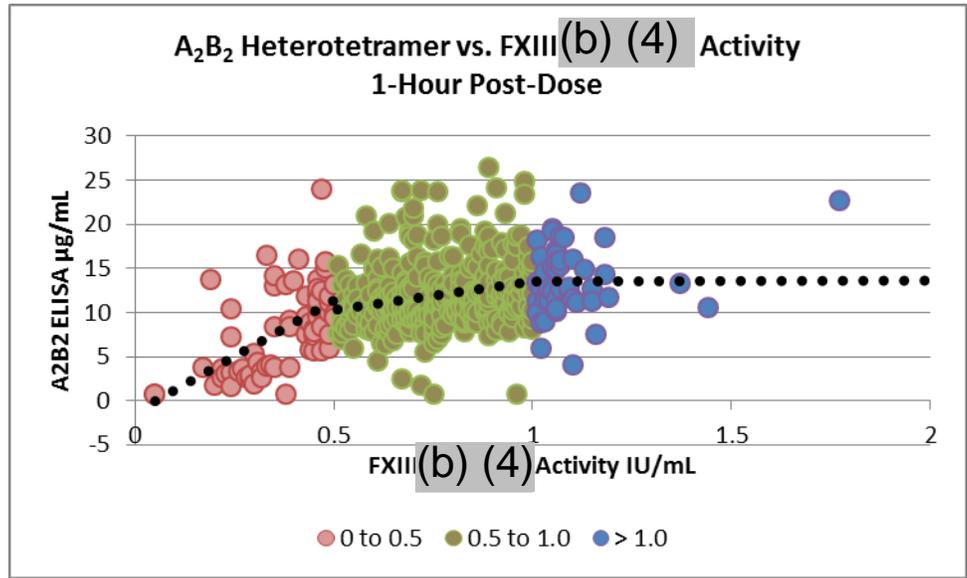
In study F13CD-1725, pre-dose and 1-hour post-dose blood samples were drawn for measurement of FXIII activity (Berichrom assay, IU/mL), A₂B₂ heterotetramer concentration ((b) (4) µg/mL), A₂ homodimer concentration ((b) (4) µg/mL), and B subunit concentration ((b) (4) µg/mL).

The following chart shows the 1-hour post-dose FXIII activity levels observed over all subjects for all study visits:



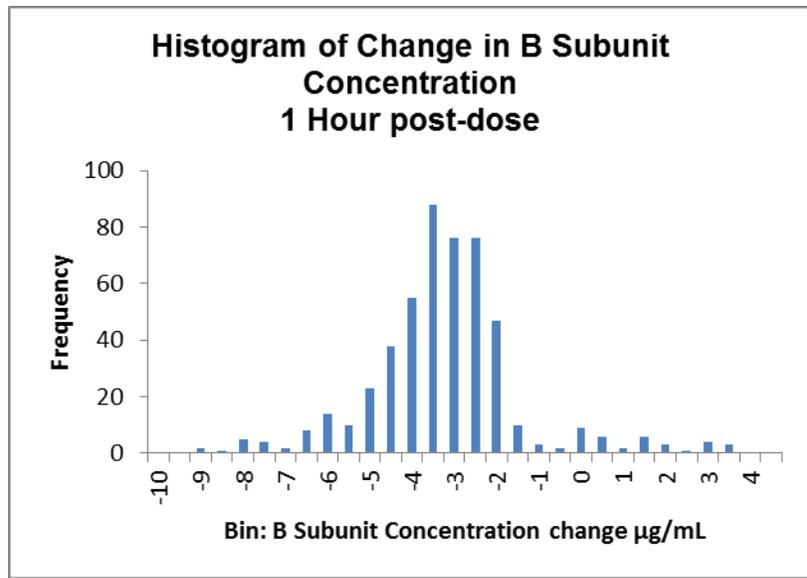
It can be seen that the 35 IU/kg dose resulted in 1-hour post-dose FXIII activity levels of approximately 1 IU/mL, as measured by the Berichrom assay.

The following chart shows the average 1-hour post-dose A₂B₂ heterotetramer concentration (i.e. the FXIII antigen level) as a function of the observed FXIII activity level, for 3 ranges of FXIII activity:



It can be seen that there is decreased dose proportionality as FXIII activity values increase toward 1 IU/mL, with loss of dose proportionality at FXIII activities above 1 IU/mL.

The following chart shows a frequency histogram of the change in B subunit concentration from the value pre-dose to the value 1-hour post-dose:



It can be seen that the B subunit concentration decreases after dosing

Reviewer’s comment: These pharmacodynamic data are consistent with the model in which there is consumption of B subunits into A₂B₂ dimer formation after dosing. This marks a fundamental difference between NovoThirteen[®] dosing and plasma-derived Factor XIII dosing: NovoThirteen[®] dosing is limited by the available B subunits for the formation of A₂B₂ dimers, whereas plasma-derived Factor XIII dosing delivers pre-formed A₂B₂ dimers, and therefore, dose proportionality for post-dose A₂B₂ concentration is to be expected (unlike the situation shown above for NovoThirteen[®]).

4.4.3 Human Pharmacokinetics (PK)

NovoThirteen[®] is only the A-subunit of Factor XIII. When injected, it is thought to combine with endogenous free B-subunits to form the A₂B₂ structure that characterizes Factor XIII. The B-subunit stabilizes the structure and results in PK parameters very similar to native Factor XIII. [See the clinical pharmacology review of Harold Boxenbaum, Ph.D.]

From the submission:

Table 3–2 Pharmacokinetic Parameters – Healthy Subjects

	Trial ID		Dose (IU/kg)	No. M; F	AUC _{0-∞} (h*IU/mL) mean (SD)	C _{max} (IU/mL) mean (SD)	V _{ss} (mL/kg) mean (SD)	CL (mL/h/kg) mean (SD)	t _{1/2} (h) mean (SD)	MRT (h) mean (SD)
Single dose	NN18 41-3788 ^b	rFXIII ^{(b) (4)}	35	50M	278 (47) ^c	0.85 (24) ^c	47 (25) ^c	0.13 (37) ^c	266 (64) ^c	372 (67) ^c
		rFXIII _N			301 (142)	0.87 (0.21) ^d	48 (12)	0.14 (0.05)	303 (195)	423 (282)
	F13-1661		30	4M; 4F ^c	207 (61)	0.80 (0.14)	45 (18)	0.15 (0.05)	219 (80)	313 (139)
	F13-1661		60	5M; 3F ^f	342 (204)	1.02 (0.14)	69 (18)	0.24 (0.16)	273 (161)	402 (232)
	NN1810-3733		12	8M	97 (45) ^c	0.28 (17) ^c	52 (29) ^c	0.12 (46) ^c	270 (60) ^c	429 (52) ^c
			35	8M	177 (30) ^c	0.77 (13) ^c	58 (21) ^c	0.20 (37) ^c	176 (37) ^c	291 (31) ^c
Multiple dose	F13-1662		12	6M; 2F	AUC _{0-24h} 16.9 (2.1)	0.87 (0.19)	-	-	346 (215)	-
	F13-1662		30	2M; 6F	AUC _{0-24h} 37.4 (5.5)	1.80 (0.25)	-	-	167 (50)	-

Source: Adapted from - sBLA 125398/0; Section 2.5 Clinical Overview , p. 17 of 42

^a N = number of subjects exposed. M = male; F = female.

^b pooled data presented (rFXIII^{(b) (4)} and rFXIII_{NN}) giving a total of 98 exposures (NN1841-3788).

^c Geometric mean (CV) in (NN1841-3788 and NN1810-3733).

^d C_{30min} (NN1841-3788).

^{e+f} Of these, 4^e and 7^f subjects contributed to the PK assessment (F13-1661).

Cross-reference: Trial 3788 (Module [M] 5.3.1.2), Trial F13-1661 (M 5.3.3.1), Trial F13-1662 (M 5.3.3.1), Trial 3733 (M 5.3.3.1)

4.5 Statistical

4.6 Pharmacovigilance

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This review was strongly influenced by the repeat-dose (b) (4) monkey study that showed durable anti-FXIII autoantibody formation in study NN205255. This finding may or may not be of importance in interpreting the results from clinical use of rFXIII_{A2}.

A characterization of the antigen epitopes recognized by these anti-FXIII autoantibodies in study NN0665-979-B showed that rFXIII_{A2} is antigenically different from plasma-derived Factor XIII in this assay.

Nonclinical studies (both *in vitro* and *in vivo*) and the phase 1 pharmacokinetic and pharmacodynamic studies showed that rFXIII_{A2} would be expected to show FXIII activity in clinical studies for FXIII congenitally-deficient patients as replacement therapy.

Therefore, this review is skewed toward the analysis of safety over the analysis of efficacy, which nevertheless has been adequately demonstrated. Studies F13CD-1725 and its extension study F13CD-3720 are the main sources for the safety database.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

This review covers data submitted from the following sources:

1. Clinical data submitted in STN 125398 for the following clinical studies:
 - a. F13-1663 US (2004) -- Safety and pharmacokinetics of rFXIII in patients with congenital factor XIII deficiency [see the Clinical Pharmacology review of Harold Boxenbaum, Ph.D.]
 - b. F13CD-1725 (2010) Europe, Canada, US – Phase 3 efficacy and safety
 - c. F13CD-3720 (Ongoing) Europe, Canada, US – Safety extension trial to the phase 3 F13CD-1725 trial
2. Nonclinical data submitted in STN125398 in the following study reports:
 - a. Study NN205255 : “NN1841 recombinant FXIII: 27 Week Intermittent Intravenous Administration Toxicity Study in the Monkey Followed by an 8 Week Reversibility Period”

- b. “Review of Histopathological Kidney Findings from Two Monkey Studies Conducted at (b) (4) and One Conducted at (b) (4) on rFXIII”
3. “Response to FDA Request Dated 2 August 2011”
4. The nonclinical study report collected by the FDA Bioresearch Monitoring team, titled “NN0665-979-B Anti-Factor XIII antibodies Determination of the Isotype and Cross reactivity of anti-FXIII Antibodies in Human plasma (EDTA) Using (b) (4)”

5.3 Table of Studies/Clinical Trials

The following table summarizes the clinical studies conducted with rFXIII A2 (NovoThirteen®):

Type of Study	Trial ID, Region (Year)	Trial and Objectives	Subjects Exposed (M/F)	Test product(s), Dosage regimen, Route of Administration	Trial Design and Type of Control	Duration of treatment	Study Status, Type of Report, Report (CTR) location
<i>Healthy subjects</i>							
BE	NN1841-3788 UK (2010)	Investigation of bioequivalence and pharmacokinetics of rFXIII(b) (4) and rFXIIIINN.	Healthy 50M	35 IU/kg rFXIII Single dose (i.v.)	A single-centre, randomized, double-blind, cross-over trial in healthy male subjects	Single-dose	Complete; Full Module 5.3.1.2, NN1841-3788
PK	F13-1661 UK (2003)	Safety and pharmacokinetics of rFXIII in healthy volunteers.	Healthy 50 (29M/21F)	rFXIII at 2, 6, 12, 30 and 60 IU/kg , or placebo Single dose (i.v.)	A randomized, placebo-controlled, single-dose double-blind trial	Single-dose	Complete; Full Module 5.3.3.1, F13-1661
PK	F13-1662 UK (2004)	Safety and pharmacokinetics of rFXIII in healthy volunteers.	Healthy 24 (13M/11F)	12 and 30 IU/kg rFXIII, or placebo Once daily for 5 consecutive days (i.v.)	A randomized, placebo-controlled, double-blind, multi-dose trial	Multi-dose 5 days	Complete; Full Module 5.3.3.1, F13-1662
PK	NN1810-3733 Japan (2010)	Safety and pharmacokinetics of rFXIII in healthy Japanese subjects	Healthy 24M	12 and 35 IU/kg rFXIII, or placebo Single dose (i.v.)	A randomized, placebo-controlled, single-dose, parallel-group, double-blind trial	Single-dose	Complete; Full Module 5.3.3.1, NN1810-3733
<i>Patients with Congenital FXIII Deficiency (CD)</i>							
PK	F13-1663 US (2004)	Safety and pharmacokinetics of rFXIII in patients with congenital	CD patients 9 (5M/4F)	2, 7, 24, 60 and 89 IU/kg rFXIII Single dose (i.v.) 2 patients at the low dose level	Escalating dose study Open -label	Single-dose	Complete; Full Module 5.3.3.2 F13-1663

Type of Study	Trial ID, Region (Year)	Trial and Objectives	Subjects Exposed (M/F)	Test product(s), Dosage regimen, Route of Administration	Trial Design and Type of Control	Duration of treatment	Study Status, Type of Report, Report (CTR) location
		factor XIII deficiency		were re-enrolled at higher dose levels			
Efficacy and safety	F13CD-1725 (2010) AT, CA, FI, FR, DE, IL, IT, ES, CH, GB, US	Confirmatory phase 3 efficacy and safety trial	CD patients 41 (23M/18F)	35 IU/kg rFXIII Monthly doses (28± 2 days) (i.v)	Multi-centre, multi-national Open-label; Single-arm	Multi-dose 52 weeks	Complete; Full Module 5.3.5.1, F13CD-1725
Safety and Efficacy	F13CD-3720 AT, CA, FI, FR, DE, IL, IT, ES, CH, GB, US	Safety extension trial to the phase 3 F13CD-1725 trial	CD patients 33 (20M, 13F) completers from F13CD-1725 *	35 IU/kg rFXIII Monthly doses (28± 2 days) (i.v)	Multi-centre, multi-national Open-label Single-arm	Multi-dose Minimum 52 weeks.	Ongoing; Interim Module 5.3.5.2, F13CD-3720 (preliminary CTR)
<i>Cardiac Surgery</i>							
PK	F13CARD-1660 DK, UK, DE	Evaluation of safety of single-dose exposure to rFXIII following cardiac surgery requiring cardiopulmonary bypass	43 cardiac surgery patients (34M/9F)	11.9, 25, 35 or 50 IU/kg rFXIII, or placebo	Multi-centre, multi-national Randomised Double-blind, placebo controlled, dose-escalation	Single-dose	Complete; Full Module 5.3.5.4, F13CARD 1660
Efficacy	NN1810-3540 CA, DK GB, US, FR, DE, IL, IT, ES, SE	Evaluation of efficacy and safety of single-dose exposure to rFXIII following cardiac surgery requiring cardiopulmonary bypass	369 cardiac surgery patients until the cut-off date for this document (30 November 2010)	17.5 or 35 IU/kg rFXIII, or placebo	Multi-centre, multi-national Randomised Double-blind, placebo controlled	Single-dose	Ongoing; Interim Safety data included Module 5.3.5.4, NN1810 3540

* To expand the safety data base, the F13CD-3720 protocol was amended to allow for inclusion of additional patients into the trial. However, no additional patients were recruited into the trial as of the cut-off date of 30 November 2010.
Source: STN125398 section 5.2 “Tabular listing of all Clinical Studies”

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

The product is a new molecular entity (NME), and therefore, a Blood Products Advisory Committee (BPAC) Meeting is required prior to licensure. A scheduled BPAC meeting for December 2011 was cancelled when it became apparent that a Complete Response (CR) letter would be issued as a result of inspection issues.

5.4.2 External Consults/Collaborations

The need for consultations was discussed, and it was decided that there is sufficient experience within OBRR to review this submission, considering the 20 years' experience OBRR has had in reviewing recombinant Factor XIII and the recent approval of plasma-derived Factor XIII. The need for consultations will be reconsidered as the review proceeds.

5.5 Literature Reviewed (if applicable)

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Titled: "A Multi-Centre, Open-Label, Single-Arm and Multiple Dosing Trial on Efficacy and Safety of Monthly Replacement Therapy with Recombinant Factor XIII (rFXIII) in Subjects with Congenital Factor XIII Deficiency"

6.1.1 Objectives (Primary, Secondary, etc.)

Primary Objective:

- To evaluate the efficacy of monthly replacement therapy with rFXIII in prevention of bleeding episodes in subjects with congenital FXIII deficiency.

Secondary Objective:

- To evaluate the safety of monthly replacement therapy with rFXIII.

6.1.2 Design Overview

Design:

Multicenter, international, open-label, single arm, historically controlled, multiple dosing phase 3 trial evaluating the efficacy and safety of monthly replacement therapy with rFXIII for routine prophylaxis of bleeding episodes associated with congenital FXIII deficiency

6.1.3 Population

The 41 enrolled and exposed subjects were diagnosed to be congenitally deficient in Factor XIII, and were either experienced or naïve to routine prophylaxis using a Factor XIII-containing product. They ranged in age from 7 to 60 years of age (median: 23

years). Males were 56% of the enrollment; females were 44%. See [Appendix 1](#) for the eligibility criteria.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Recombinant FXIII was supplied as a sterile lyophilized powder for injection in single use vials of 15 mg (2505 IU) per vial in a concentration of 835 IU/mL when reconstituted. Each vial was reconstituted in 3.2 mL sterile water for injection. The reconstituted preparation is a clear, colorless to pale yellow isotonic solution, with a pH of approximately 8.0.

Each subject underwent a 4 week run-in period during which no Factor XIII-containing product was administered to the subject to allow for a wash-out period.

The first dose is given at Visit 2. All doses are given during clinic visits, which occurred every 28 ± 2 days, for 52 weeks.

The dose was 35 IU/kg intravenously, delivered at a rate of 1-2 mL per minute.

The treatment of acute bleeding episodes was by local standard-of-care.

6.1.5 Directions for Use

The dose was 35 IU/kg intravenously, delivered at a rate of 1-2 mL per minute.

6.1.6 Sites and Centers

The following table shows the distribution of the enrollment among countries by gender and age:

Country	Number of Subjects	Ages of Females (years)	Ages of Males (years)
Austria	1	41	
Canada	3	8	7, 10
Finland	2	48	52
France	1		41
Germany	6	23, 57	12, 16, 17, 25
Israel	8	8, 26, 29, 35, 50	18, 27, 55
Italy	1	46	
Spain	2		7, 34
Switzerland	2	23	49
United Kingdom	5	11, 19, 23	11, 60
USA	10	10, 16, 25	8, 12, 13, 22, 22, 23, 43

6.1.7 Surveillance/Monitoring

The schedule of events for monitoring is given in [Appendix 1](#).

6.1.8 Endpoints and Criteria for Study Success

6.1.9 Statistical Considerations & Statistical Analysis Plan

The development of the **historical control bleed rate** is described in a report titled “Retrospective Data Collection in Patients with Congenital Factor XIII-deficiency.” This report is intended to describe the features, medical needs and treatment patterns of patients with congenital FXIII-deficiency. It is based on information collected through questionnaires compiling data from medical records of congenitally FXIII-deficient patients at 35 sites in 13 countries in Europe, the Middle East, Brazil, Australia, and South Africa.

The following table shows the geographic representation of the responding centers:

Table 7–1 Summary of Responding Centres

Country	Number of Subjects N (%)	N (Number of Centres %)
Total	92 (100.0 %)	35 (100.0 %)
Australia (AU)	1 (1.1 %)	1 (2.9 %)
Austria (AT)	2 (2.2 %)	1 (2.9 %)
Brazil (BR)	1 (1.1 %)	1 (2.9 %)
Croatia (HR)	2 (2.2 %)	1 (2.9 %)
Denmark (DK)	2 (2.2 %)	1 (2.9 %)
Germany (DE)	27 (29.3 %)	16 (45.7 %)
Israel (IL)	12 (13.0 %)	1 (2.9 %)
Poland (PL)	8 (8.7 %)	1 (2.9 %)
Saudi Arabia (SA)	7 (7.6 %)	2 (5.7 %)
Serbia and Montenegro (CS)	4 (4.3 %)	1 (2.9 %)
South Africa (ZA)	4 (4.3 %)	3 (8.6 %)
Spain (ES)	15 (16.3 %)	2 (5.7 %)
Switzerland (CH)	7 (7.6 %)	4 (11.4 %)

“Source: Adapted from - sBLA 125398/0; Module 5.3.5.1.12 F13CD-QUEST
Clinical Report, p.20 of 37”

The following table gives the demographic data of the questionnaire subject:

Table 7–2 Demographic Data at the Time of Data Collection

		Number of subjects N (%)	Date of Death
Population	N	92	
Age (Year)*	N	91	
	Mean	26.7	
	Median	25.0	
	Min; Max	0.1; 71.0	

Body weight (kg)	N	73	
	Mean	59.0	
	Median	61.0	
	Min; Max	4.0 ; 130.0	
Gender	Female	45 (48.9 %)	
	Male	47 (51.1 %)	
Ethnic Origin	Arab	7 (7.6 %)	
	Asian	1 (1.1 %)	
	Black	4 (4.3 %)	
	Other	3 (3.3 %)	
	White	77 (83.7 %)	
Alive Today	N	92	
	Yes	87 (94.6 %)	
	No	1 (1.1 %)	10081 985
	Unknow n	4 (4.3 %)	

“Source: Adapted from - sBLA 125398/0; Module 5.3.5.1.12 F13CD-QUEST
Clinical Report, p.21 of 37”

The following table gives the age at first congenital FXIII-deficiency diagnosis and the reasons for initiating the diagnostic procedures for the questionnaire subjects:

Table 7–3 Summary of Age and Reason for Diagnosis

		Number of subjects N (%)
Population	N	92
Age at first diagnosis (Year)*	N	80
	Mean	7.9
	Median	3.5
	Min; Max	0.0 ; 53.0
Age at first diagnosis (Year)*	N	80
	0 years	27 (33.8 %)
	1-5 years	20 (25.0 %)
	6-10 years	9 (11.3 %)

	11-15 years	9 (11.3 %)
	16-20 years	7 (8.8 %)
	21-30 years	4 (5.0 %)
	31-40 years	3 (3.8 %)
	>50 years	1 (1.3 %)
	Unknown	12
Reason for diagnostic procedure	N	90
	Bleeding	75 (83.3 %)
	Bleeding+Family history	7 (7.8 %)
	Family history	7 (7.8 %)
	Preoperative screening	1 (1.1 %)
	NA**	2
Patients with	1 reason	83 (92.2 %)
	2 reason(s)	7 (7.8 %)

*Data is not available for all patients; 0.01 years was assigned for age recorded as "newborn", "at birth" or "after birth".

**NA means that the age at first diagnosis is provided but the reason for the diagnostic procedure is omitted

“Source: Adapted from - sBLA 125398/0; Module 5.3.5.1.12 F13CD-QUEST Clinical Report, p.22 of 37”

The following table summarizes the disease characteristics of these subjects:

Table 7–4 Summary of FXIII Status at Diagnosis

		Number of subjects N (%)
FXIII-deficiency subtype	A-subunit	39 (42.4 %)
	B-subunit	2 (2.2 %)
	A+B-subunit	4 (4.3 %)
	Unknown	47 (51.1 %)
	Total	92 (100.0 %)
FXIII activity level*	Yes	82 (89.1 %)
	No	10 (10.9 %)
Minimal FXIII activity (%)	N	78

	Mean	7.1
	Median	3.5
	Min; Max	0.0 ; 55.0
Minimal FXIII activity (%)	N	78
	<1%	9 (11.5 %)
	1-5%	43 (55.1 %)
	6-10%	15 (19.2 %)
	11-25%	6 (7.7 %)
	26-50%	2 (2.6 %)
	>50%	3 (3.8 %)
	Unknown	5
FXIII antigen level measured	Yes	12 (13.0 %)
	No	73 (79.3 %)
	NA	7 (7.6 %)
FXIII antigen levels**	N	12
	Mean	3.8
	Median	3.0
	Min; Max	0.0 ; 14.0
Clot solubility test to confirm diagnosis	N	92 (100.0 %)
	Yes	32 (34.8 %)
	No	32 (34.8 %)
	NA	28 (30.4 %)

*FXIII activity levels reported is the minimum value of FXIII activity/FXIII residual activity level. Hardcoded: Patients (b) (6) = 5% (orig. 0.5 IU) (b) (6) = 3% (orig. 0.3 IU) (b) (6) = 4% (orig. 0.04 IU). 4 patients have Yes in FXIII level measured at first diagnosis - but no value

**Data are not available for all patients. Patient (b) (6) has an antigen level of 0.05 with NA as unit. The result has been interpreted as 0.05%.

“Source: Adapted from - sBLA 125398/0; Module 5.3.5.1.12 F13CD-QUEST Clinical Report, p.23 of 37”

The following table summarizes the bleeding history of these subjects:

Table 7–5 Summary of Bleeding History

		Patients N (%)	Bleeding Events N
Population	N	92	
No bleeding yet		4 (4.3 %)	
Age at first	N	84	

bleed (Year)*			
	Mean	1.9	
	Median	0.0	
	Min; Max	0.0 ;19.0	
Age at first bleed*	N	84	
	0 years	57 (67.9 %)	
	1-5 years	16 (19.0 %)	
	6-10 years	6 (7.1 %)	
	11-15 years	4 (4.8 %)	
	16-20 years	1 (1.2 %)	
	Unknown	8	
Cause of first bleed	N	87	
	Spontaneous	57 (65.5 %)	
	Surgical	5 (5.7 %)	
	Traumatic	12 (13.8 %)	
	Post surgical bleeding in the newborn period	13 (14.9 %)	
Site of first bleed**	N	86	
	Central and peripheral nervous system	8 (9.3 %)	
	Ears, eyes, nose, throat, neck	1 (1.2 %)	
	Gastrointestinal system	4 (4.7 %)	
	Mouth and oral mucosa	4 (4.7 %)	
	Intraabdominal	2 (2.3 %)	
	Musculoskeletal system	7 (8.1 %)	
	Surgery related	3 (3.5 %)	
	Skin	24 (27.9 %)	
	Umbilical	57 (66.3 %)	
Patients with 2 sites at first bleed	N	14	
Patients with 3 sites at first bleed	N	5	

Sites of bleed before first FXIII exposure	N	60	270
	Central and peripheral nervous system	17 (28.3 %)	32
	Ears, eyes, nose, throat, neck	3 (5.0 %)	8
	Gastrointestinal system	6 (10.0 %)	17
	Intra-abdominal	4 (6.7 %)	6
	Mouth and oral mucosa	5 (8.3 %)	18
	Musculoskeletal system	19 (31.7 %)	53
	Renal & vertebral haematoma	1 (1.7 %)	2
	Skin	20 (33.3 %)	100
	Surgery related	2 (3.3 %)	4
	Umbilical	30 (50.0 %)	30
Bleeding sites reported	N	60	
	1	28	
	2	20	
	3	10	
	4	1	
	5	1	

*Data are not available for all patients; 0.01 years was assigned for age recorded as "newborn", "at birth" or "after birth".

**A patient may have >1 site of first bleed.

“Source: Adapted from - sBLA 125398/0; Module 5.3.5.1.12 F13CD-QUEST
Clinical Report, p.25 of 37”

The following table summarizes bleeding history by the subject’s disease severity:

Table 7–6 Summary of Bleeding History by Severity

	Number of subjects N (%)
Population	92
Patients with severe deficiency, total*	52 (100.0 %)
Patients with bleeding before first FXIII-exposure	51 (98.1 %)

Patients with CNS bleedings	20 (38.5 %)
Patients with minimal FXIII activity >5%	26 (100.0 %)
Patients with bleeding before first FXIII-exposure	23 (88.5 %)
Patients with CNS bleedings	6 (23.1 %)

*Severe defined as $\leq 5\%$ FXIII activity

“Source: Adapted from - sBLA 125398/0; Module 5.3.5.1.12 F13CD-QUEST Clinical Report, p.26 of 37”

The following table summarizes the medical histories of CNS bleeds among the subjects:

Table 7–7 Summary of History of CNS Bleeds

Population	N	92
Patients with history of CNS bleeds	Yes	26 (28.3 %)
	Unknown	1 (1.1 %)
	No	65 (70.7 %)
Number of CNS bleeding episodes	Number of patients	Number of bleedings
	1	14 (53.8 %)
	2	6 (23.1 %)
	2.5	1 (3.8 %)
	3.5	1 (3.8 %)
	5	2 (7.7 %)
	10	1 (3.8 %)
	Unknown	1 (3.8 %)
	Cause of CNS bleeds	Post-trauma
Spontaneous		20 (76.9 %)
Spontaneous and Post-trauma		4 (15.4 %)
Age at first CNS/ICH*	N	20
	Mean	8.1
	Median	2.0
	Min; Max	0.3 ; 53.0

*6 subjects with CNS bleeds did not have a recorded age at first CNS bleeding episode.

“Source: Adapted from - sBLA 125398/0; Module 5.3.5.1.12 F13CD-QUEST Clinical Report, p.27 of 37”

Table 7–8 Summary of Prophylaxis Treatment

		Number of subjects N (%)
Population		92

Patients with a history of regular Prophylaxis (historic or current)	Yes	69 (75.0 %)	
	No	23 (25.0 %)	
Age at start of prophylaxis*	N	48	
	Mean	14.8	
	Median	10.0	
	Min; Max	0.0 ;63.0	
Age at start of prophylaxis*	N	48	
	0 years	8 (16.7 %)	
	1-5 years	12 (25.0 %)	
	6-10 years	5 (10.4 %)	
	11-15 years	5 (10.4 %)	
	16-20 years	5 (10.4 %)	
	21-30 years	6 (12.5 %)	
	31-40 years	2 (4.2 %)	
	41-50 years	3 (6.3 %)	
	>50 years	2 (4.2 %)	
	Unknown	2	
	Patients currently receiving prophylactic treatment**	Total	45 (100.0 %)
		Cryoprecipitate	2 (4.4 %)
Fibrogammin P		41 (91.1 %)	
Other FXIII concentrate		2 (4.4 %)	
Dose per kg for patients treated with prophylactic Fibrogammin P	N	49	
	Mean	20.1	
	Median	14.9	
	Min; Max	5.7 ;64.1	

*Data are not available for all patients; 0.01 years was assigned for age recorded as "newborn", "at birth" or "after birth".

**Each subject can have up to 3 types of prophylaxis.

***For patients on current prophylaxis

“Source: Adapted from - sBLA 125398/0; Module 5.3.5.1.12 F13CD-QUEST
Clinical Report, p.29 of 37”

Table 7–9 Summary of Breakthrough Bleeds during Prophylaxis

	Regular Prophylaxis	
Patients with history of prophylaxis		69

Patients with available bleeding information Total		64 (100.0 %)
Patients with history of breakthrough bleeds	Yes	17 (26.6 %)
	No	47 (73.4 %)
Anatomical bleeding site*		
	Genito-urinary system	3
	Musculoskeletal system	9
	Skin	12
Number of patients with		
	one site	10
	two sites	7
Number of bleeds per patient year	N	60
	Mean	0.3
	Median	0.0
	Min; Max	0.0 ;7.0
Total number of bleeds		20.0
Age (Years)*	N	59
	Mean	28.6
	Median	28.0
	Min; Max	2.8 ;71.0
Total (patient years)		1690.3

*7 Patients had a total of 2 bleeding sites

**Data is not available for all patients included in the calculation of number of bleed per year.

“Source: Adapted from - sBLA 125398/0; Module 5.3.5.1.12 F13CD-QUEST
Clinical Report, p.30 of 37”

Table 7–10 Summary of On-demand Treatment

		Number of subjects N (%)
Patients without prophylactic treatment	N	23
Patients with on-demand treatment only*	Yes	20 (87.0 %)
	No	3 (13.0 %)
Number of bleeds per patient year*	N	16
	Mean	2.9
	Median	2.0
	Min; Max	0.0 ; 12.0

Total Number of Bleeds*		46.5
CNS Bleeding	Yes	1 (4.3 %)
	No	22 (95.7 %)
Age (patient years)*	N	16
	Sum	506.5
	Mean	31.7
	Median	32.0
	Min; Max	5.0 ; 63.0
Patients receiving more than one FXIII containing product**		1
Patients receiving only one FXIII containing product	Total	19
	Cryoprecipitate	2 (10.5 %)
	FFP	7 (36.8 %)
	Fibrogammin P	9 (47.4 %)
	NA	1 (5.3 %)

*Only patients with no current prophylaxis included.

**The following treatments are excluded: Thrombin, Fibrinogen and Cyclocapron.

“Source: Adapted from - sBLA 125398/0; Module 5.3.5.1.12 F13CD-QUEST Clinical Report, p.32 of 37”

Table 7–11 Summary of Bleeding Frequency by Treatment Modality

		Prophylaxis	On-demand
Total Number of Patients		69	23
Number of Patients	With Bleeds	17*	12
	Without Bleeds	47	4**
	With Unknown Bleeding History	5	7
Number of Patients use for frequency calculation***		60	16
Number of Bleeds per Year****	Total	20.0*****	46.5*****
	Range	0- 7	0-12
	Average	0.3 (20.0/60)	2.9 (46.5/16)

**Only 13 patients have data available on number of bleedings.

** Only 4 patients have at least one year exposure to FXIII.

*** Excluded patients showed incomplete data for calculation.

**** Counted as total for those patients used for the frequency calculation.

***** All types of bleeds (both treatment requiring and non-treated).

***** Only treatment requiring bleeds.

“Source: Adapted from - sBLA 125398/0; Module 5.3.5.1.12 F13CD-QUEST Clinical Report, p.33 of 37”

Listing 7 After initiation of treatment - On-demand Treatment

Patient Code	On-demand treatment	Type of treatment	Dose	Unit	No. doses	Dose interval	Average number of bleedings per year requiring on demand treatment	Date of last on-demand treatment
(b) (6)	YES	Fresh Frozen Plasma	1	Units	6	NA	11	27-Jun-2000
	YES	Cryoprecipitate	5	NA	14	NA	5	xxxx2005
	YES	Fibrogammin P	250	Units	1	NA	0	3-Jan-2001
	YES	NA	NA	NA	NA	NA	0	14-Jun-2005
	NO	Fibrogammin P	625	Units	3	24 hour	0	NA
	YES	NA	NA	NA	3	24 hour	NA	NA
	NO	Fibrogammin P	2500	Units	1	NA	NA	NA
	YES	Fibrinogen	6000	mg	1	NA	0.5	5-May-2000
	YES	NA	NA	NA	NA	NA	unknown	NA
	YES	NA	NA	NA	NA	NA	12	NA
	YES	NA	NA	NA	NA	NA	0	11-May-1981
	YES	NA	NA	NA	NA	NA	2	NA
	NO	NA	NA	NA	NA	NA	0	NA
		NA	NA	NA	NA	NA		
	YES	NA	NA	NA	NA	NA	2-6 per year	13-Feb-1991
		FFP	3	Units	1	NA		
	YES	Fibrogammin P	387.5	Units	1 - 3	24 hour	1	xxxx2004
		Fibrogammin P	1250	Units	1	NA		
	YES	NA	NA	NA	NA	NA	2-3	17-Oct-2004
		Fibrogammin P	500	Units	1	NA		
	YES	Fibrogammin P	1250	Units	1	NA	NA	NA
		FFP	NA	NA	NA	NA		
		Thrombin	NA	NA	NA	NA		
	YES	NA	NA	NA	NA	NA	3	11-Nov-2001
		FFP	NA	NA	NA	NA		
	YES	Fibrogammin P	1000	Units	1	NA	NA	xxJan-2005
		FFP	NA	NA	NA	NA		
YES	NA	NA	NA	NA	NA	NA	xxxx2003	
	FFP	NA	NA	NA	NA			
YES	Fibrogammin P	2400	Units	1	NA	2	1-Jun-2004	
	Cryoprecipitate	4	Units	4	Daily			

Patient Code	On-demand treatment	Type of treatment	Dose	Unit	No. doses	Dose interval	Average number of bleedings per year requiring on demand treatment	Date of last on-demand treatment
(b) (6)	YES	NA	NA	NA	NA	NA	1.5	26-May-2004
		Cryoprecipitate	4	Units	1	NA		
	YES	FFP	unkno wn	NA	2	NA	2	xxJan-2004
		FFP	NA	NA	NA	NA		
		Cyklokapron	500	mg	NA	every 8 hours		

“Source: Adapted from - sBLA 125398/0; 5.3.5.1.12 F13CD-QUEST Selected Listings, p.26 of 26”

FDA made the following request for information on September 22, 2011:

Please justify the inclusion of the two "outliers" in the calculation of the historical bleeding control.

Novo Nordisk responded to this request for information in STN125398.09 as follows:

The two patients from the historical control calculation with 11 and 12 bleeds per year are not considered outliers but simply patients with high values. In haemophilia (A and B), for example, the bleeding rate is to a large extent patient specific and variable with some patients bleeding frequently and other patients almost never bleed. **There is no inherent reason to believe that this variation in bleeding pattern is different in patients with FXIII congenital deficiency.**(emphasis added)

The other patients from the historical control calculation did bleed less but there were patients with 4 and 5 bleeds per year.

It should be taken into consideration that patients known to have (or be pre-disposed for) a high bleeding rate while on an on-demand treatment regimen, often will be put on prophylactic treatment and therefore will be underrepresented in the on-demand population.

This tendency to put high-frequent bleeders on prophylactic treatment dilutes their prevalence in the on-demand population and causes such high-frequent bleeders to appear as “outliers” in the (remaining) actual on-demand population.

Reasons for not moving high-frequent bleeders from an on-demand treatment regimen to a prophylactic regimen may sometimes not be rooted in a clinical/medical rationale but due to socioeconomic factors.

In the entire historic dataset including the prophylactically treated patients there are for example 4 black patients, 2 from South Africa, 1 from Brazil and 1 from Israel. Of these four patients only the patient from Israel is treated prophylactically, while the other 3 black patients are on-demand treatment.

The patient with 11 bleeds per year is a 16 year old black male patient from Brazil. The other frequently bleeding patient is a 52 year old male from Spain who is treated at a centre with 13 patients of which 6 are treated with on-demand. This could suggest that the two frequently bleeding patients not on prophylaxis are on on-demand treatment due to socio-economic factors.

It is therefore considered that these two patients with highest bleeding frequencies can be expected in a representative on-demand population and therefore should be included in the estimate of the historical on-demand rate.

Excluding these two patients leads to an estimated historical annual on-demand bleeding rate of 1.68 for the remaining 14 patients. This bleeding rate estimate will be biased towards a too low value, since it corresponds to substituting the two most frequent bleeders with subjects having a bleeding rate equal to the mean rate of the other 14 subjects. It is still considerably higher than the bleeding rate observed in the pivotal trial.

Having 1.68 as the historical on-demand bleeding rate would not change the efficacy conclusions from the trial, including for the primary endpoint. (emphasis added)

Reviewer's Comment:

Novo Nordisk should be asked to amend the statistical analysis plan by omitting the data from these two subjects in the historical control annualized bleed rate and to make corresponding changes in the labeling.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

6.1.10.1.3 Subject Disposition

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

6.1.11.2 Analyses of Secondary Endpoints

6.1.11.3 Subpopulation Analyses

6.1.11.4 Dropouts and/or Discontinuations

6.1.11.5 Exploratory and Post Hoc Analyses

6.1.12 Safety Analyses

6.1.12.1 Methods

The following table shows the extent of exposure to rFXIIA₂ in F13CD-1725:

Table 12–1 Exposure to Trial Drug

Number of subjects	41
Number of doses per subjects	
N	41
Mean (SD)	11.5 (3.59)
Median	13
Min ;Max	2 ; 14
Number of late doses	
N	3
Mean (SD)	1.0 (0.00)
Median	1
Min ;Max	1; 1
Delay of late doses (days)	
N	3
Mean (SD)	18.3 (9.24)
Median	13
Min ;Max	13 ; 29

Source: STN125398/OS F13CD-1725 Clinical Trial Report, p. 57 of 705

All reported treatment-emergent adverse events (TEAEs) for study F13CD-1725 are given in [Appendix 3](#), where they are classified as nonserious or serious, and by severity.

The adverse event “pollakiuria” was reported for two UK subjects [subject (b) (6) a 23 y.o. female, and subject (b) (6) a 19 y.o. female who withdrew after visit 11 (week 28) due to pregnancy].

[Subject 28101](#)

At visit 8, subject (b) (6) is reported to have the adverse events pollakiuria, vomiting, diarrhoea, micturition urgency, and depressed mood. Subject (b) (6) had prolonged coagulation test results (Thrombin Time, Prothrombin Time, activated Partial Thromboplastin Time), as well as elevated Fibrinogen levels over the entire course of the study, as shown in the following table:

Subject (b) (6) Abnormal Coagulation Test Results

Date of Dosing	Visit	Laboratory Parameter	Result in original Units	Reference Range	Original Unit	Flag
17-Nov-08	Screening	APTT	22.7	22.8 - 31	seconds	H
		Thrombin time	21.8	14.5 - 18.5	seconds	H
15-Dec-08	Baseline (Week 0)	Thrombin time	20.2	14.5 - 18.5	seconds	H
30-Dec-08	Week 2	Fibrinogen	557	200 - 400	mg/dL	H
9-Feb-09	Week 8	Fibrinogen	416	200 - 400	mg/dL	H
9-Mar-09	Week 12	Thrombin time	23.4	14.5 - 18.5	seconds	H
02-Apr-09	Week 16	Thrombin time	22.4	14.5 - 18.5	seconds	H
25-Jun-09	Week 28	APTT	31.6	22.8 - 31	seconds	H
		Thrombin time	24.8	14.5 - 18.5	seconds	H
14-Oct-09	Week 44	Prothrombin Time	12.4	9.7 - 12.3	seconds	H
		Thrombin time	20	14.5 - 18.5	seconds	H
10-Nov-09	Week 48	APTT	31.6	22.8 - 31	seconds	H
		Thrombin time	20.2	14.5 - 18.5	seconds	H
08-Dec-09	Week 52	Thrombin time	18.8	14.5 - 18.5	seconds	H

Subject (b) (6) Abnormal Hematology Results

17-Nov-08	Screening	Thrombocytes	365	150 - 450	10 ⁹ /L	L
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		Erythrocytes	5.56	3.8 - 4.8	10 ⁶ /L	H
15-Dec-08	Baseline (Week 0)	Thrombocytes	297	150 - 450	10 ⁹ /L	L
		Erythrocytes	5.57	3.8 - 4.8	10 ⁶ /L	H
30-Dec-08	Week 2	Erythrocytes	5.23	3.8 - 4.8	10 ⁶ /L	H
14-Jan-09	Week 4	Erythrocytes	5.58	3.8 - 4.8	10 ⁶ /L	H
09-Feb-09	Week 8	Erythrocytes	5.60	3.8 - 4.8	10 ⁶ /L	H
09-Mar-09	Week 12	Erythrocytes	5.28	3.8 - 4.8	10 ⁶ /L	H
02-Apr-09	Week 16	Erythrocytes	5.54	3.8 - 4.8	10 ⁶ /L	H
29-Apr-09	Week 20	Erythrocytes	5.42	3.8 - 4.8	10 ⁶ /L	H
28-May-09	Week 24	Erythrocytes	5.19	3.8 - 4.8	10 ⁶ /L	H
25-Jun-09	Week 28	Erythrocytes	5.37	3.8 - 4.8	10 ⁶ /L	H
23-Jul-09	Week 32	Erythrocytes	5.18	3.8 - 4.8	10 ⁶ /L	H
20-Aug-09	Week 36	Erythrocytes	5.73	3.8 - 4.8	10 ⁶ /L	H
16-Sep-09	Week 40	Erythrocytes	5.31	3.8 - 4.8	10 ⁶ /L	H
14-Oct-09	Week 44	Erythrocytes	5.35	3.8 - 4.8	10 ⁶ /L	H
10-Nov-09	Week 48	Erythrocytes	5.23	3.8 - 4.8	10 ⁶ /L	H
08-Dec-09	Week 52	Erythrocytes	5.27	3.8 - 4.8	10 ⁶ /L	H

Subject (b) (6) 19 y.o. female

Subject (b) (6) had a heterozygous missense mutation in the F13B gene. (b) (4) results for FXIII B-subunits showed that this subject did not appear to have abnormally low levels of B-units. The B-subunits were functionally capable of binding to A-subunits as reflected in reduced levels of B-subunits and increased levels of A₂B₂ following injection of rFXIII.

On 23-JUN-2009 subject (b) (6) was hospitalized after a traffic accident. Injuries included: possible head injury, nose swollen, small laceration to the lip. No loss of consciousness and vital signs were normal. As prophylaxis, Fibrogammin P 1250 units

was administered, with FXIII level increased to 59 % and a minor bleeding resolved. Paracetamol and codeine phosphate started for pain management. The patient was admitted for overnight observation in hospital. The adverse event “pollakiuria” is listed as occurring during June 2009 with no further information.

Subject (b) (6) Abnormal Coagulation Test Results

Date of Dosing	Visit	Laboratory Parameter	Result in original Units	Reference Range	Original Unit	Flag
19-Nov-08	Screening	Thrombin time	23	14.5 - 18.5	seconds	H
15-Dec-08	Baseline (Week 0)	APTT	33.8	22.8 - 31	seconds	H
		Thrombin time	21	14.5 - 18.5	seconds	H
12-Jan-09	Week 4	APTT	31.2	22.8 - 31	seconds	H
		D dimer	>14400	0 -499	ng/mL	H
10-Feb-09	Week 8	APTT	31.6	22.8 - 31	seconds	H
01-Apr-09	Week 16	APTT	34.8	22.8 - 31	seconds	H
		Thrombin time	23.8	14.5 - 18.5	seconds	H
30-Apr-09	Week 20	APTT	32.4	22.8 - 31	seconds	H
25-Jun-09	Week 28	APTT	33.3	22.8 - 31	seconds	H
		Thrombin time	25.7	14.5 - 18.5	seconds	H
23-Jul-09	Week 32	APTT	31.3	22.8 - 31	seconds	H

6.1.12.2 Overview of Adverse Events

A listing of all treatment-emergent adverse events reported for study F13CD-1725 arranged by body system and classified by seriousness and severity is presented in [Appendix 3](#).

Table 12–2 Overview of Treatment-emergent Adverse Events - Full Analysis Set

	rFXIII 35 IU/Kg	
	N (%) Subjects	Events
Number of Subjects	41	
All Adverse Events	32(78.0)	231

Serious Adverse Events	6(14.6)	8
Adverse Events by Severity		
Severe	3(7.3)	3
Moderate	18(43.9)	37
Mild	29(70.7)	191
Adverse Events by Relationship		
Probably or Possibly related	9(22.0)	13
Unlikely Related to trial product	30(73.2)	210
Missing	2(4.9)	8
Adverse Events leading to Withdrawal*	4(9.8)	5

N: Number of subjects with adverse events.

#: Percentage of subjects with adverse event. E: Number of adverse events.

* Subjects (b) (6) were withdrawn from treatment due to observation of non-neutralising antibodies. Subject (b) (6) was withdrawn due to worsening leukopenia and worsening neutropenia.

Source: Original BLA 125398; Clinical Study Report module 5.3.4.3, p.59

Table 12–3 Treatment-emergent Adverse Events with Possible or Probable Relation to Trial Product - Full Analysis Set

Subject ID	Age*	Preferred term	Severity	Serious	Latency (days)**	Relationship	Outcome
(b) (6)	7	Antibody test positive	Mild	Y	14	Probable	Recovered
	25	Pain in extremity	Mild	N	22	Possible	Not recov.***
	26	Headache	Mild	N	0	Possible	Recovered
	8	Leukopenia****	Mild	N	32	Possible	Recovered
		Neutropenia****	Mild	N	32	Possible	Recovered
	7	Incorrect dose administered	Mild	N	0	Probable	Recovered

(b) (6)		Incorrect dose administered	Mild	N	0	Probable	Recovered
		Antibody test positive	Severe	N	28	Probable	Recovered
	60	Incorrect dose administered	Mild	N	0	Probable	Recovered
	16	Antibody test positive	Mild	Y	16	Possible	Recovered
	14	Antibody test positive	Mild	Y	16	Possible	Recovered
	8	Injection site pain	Mild	N	2	Possible	Recovered
		Fibrin D dimer increased	Mild	N	14	Probable	Recovered

SOC: System Organ Class

PT: Preferred Term

Not recov.: Not recovered

* Age at baseline

**Days since the preceding dose of rFXIII

*** Outcome as recorded at the end-of-trial visit approximately two months after onset of the event

**** Worsening of mild neutropenia initially diagnosed before first trial drug administration.

Source: Original BLA 125398; Clinical Study Report module 5.3.4.3, p.60

6.1.12.3 Deaths

There were no deaths during study F13CD-1725.

6.1.12.4 Nonfatal Serious Adverse Events

Table 12-4 Listing of Treatment-emergent Serious Adverse Events by Subjects -Full Analysis Set

Subject ID	age	Preferred term	Severity	Latency (days)**	Relationship	Outcome
(b) (6)	7	Antibody test positive	Mild	15	Probable	Recovered
	57	Diverticulitis	Moderate	3	Unlikely	Recovered
	55	Non-cardiac chest pain	Mild	23	Unlikely	Recovered
		Headache	Mild	24	Unlikely	Recovered

(b) (6)	19	Road traffic accident	Moderate	28	Unlikely	Recovered
	16	Antibody test positive	Mild	17	Possible	Recovered
	14	Small intestinal obstruction	Severe	4	Unlikely	Recovered
		Antibody test positive	Mild	17	Possible	Recovered

SOC: System Organ Class PT: Preferred Term

* Age at baseline

** Days since the preceding dose of rFXIII

Source: Original BLA 125398; Clinical Study Report module 5.3.4.3, p.61

6.1.12.5 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) have been identified from the nonclinical studies that should be evaluated in clinical studies. The AESI include the following:

1. Potential for neutralizing anti-FXIII antibody formation
2. Potential for renal toxicity
3. Potential for thromboembolism

There were no thromboembolic adverse events during study F13CD-1725.

Four subjects were identified as repeat reactive in the anti-FXIII antibody monitoring in study F13CD-1725. The details on these 4 subjects are contained in MedWatch forms submitted to IND 10674 and in information submitted in this BLA. The following gives a chronology of these 4 cases:

Subject ID: (b) (6) 14 y.o. male (sibling to subject (b) (6))

Date	Event
3/4/2009	First Dose
3/9/2009	Small intestine obstruction
3/20/2009	Anti-FXIII (b) (4) positive Titer 2.5
3/27/2009	“ongoing bleeding into his bony cyst and was treated with cryo-precipitate and transiently responding to FFP (fresh frozen plasma). However after three days of receiving treatment the patient would have painful episodes, which was suggestive of inhibitor development.”
4/3/2009	Second and last dose; Anti-FXIII (b) (4) positive Titer 2.3
4/29/2009	Anti-FXIII (b) (4) positive Titer 2.3; clot solubility test showed no lysis.

5/26/2009	Anti-FXIII (b) (4) positive Titer 2.0
7/25/2009	“Between 26-JUN-2009 (visit 7) and 25-JUL-2009 (visit 8): Antibody became undetectable. There was never detectable inhibitory effect, or detectable change in factor recovery (post-dose level) or half-life (predose levels). Since visit 8- The patient's antibody screen has been "LTR" or less than reference at all visits”
5/27/2010	“a lysis assay with and without a 1:1 mix to check for inhibitors was performed and he had clot lysis on a 1:1 mix, suggesting an inhibitor ”
6/4/2010	“PRE-cryoprecipitate infusion (after 11 units cryoppt the prior week):Factor XIII functional ... 12% of pooled normal control (0.12u/ml). 1:1 mixing study NEGATIVE.”
	“POST cryoppt infusion (11 units):Factor XIII level 31%, i.e. 0.31 U/ml. Inhibitor screen negative. The patient had LYSIS on a clot lysis assay one week after 11 u cryoppt infusion.”
6/10/2010	In IND 10674 amend 72 MEDWATCH sponsor states “The event of suspected inhibitor has an onset almost 12 months after exposure to trial drug. The previously reported antibody towards FXIII was of transient nature and reportedly the patient recovered 10 months ago. Since then, the patient has received ongoing treatment with cryoprecipitate. The inhibitor formation has not been confirmed by testing. Results are pending.”
7/25/2010	“ the patient was considered as recovered from the event FXIII antibody development. ”

Source: IND 10674 amend 76 MEDWATCH; STN125398 Listing 14.3.4.8: Listing of Positive Laboratory Test Results : Immunology - Antibody specific -Full Analysis Set p. 355 of 705

Subject ID: (b) (6) 16 y.o. female (sibling to subject (b) (6))

Date	Event
3/4/2009	First Dose
3/20/2009	Anti-FXIII (b) (4) positive Titer 2.6
4/3/2009	Second and Last Dose; Anti-FXIII (b) (4) positive Titer 2.3
4/23/2009	Anti-FXIII (b) (4) positive; Titer 2.6; clot solubility test showed no lysis.
4/29/2009	Anti-FXIII (b) (4) positive Titer 2.3; clot solubility test showed no lysis.
5/26/2009	Anti-FXIII (b) (4) positive Titer 2.3
6/26/2009	Anti-FXIII (b) (4) positive Titer 2.6
7/25/2009	Anti-FXIII (b) (4) positive Titer 2.6
9/12/2009	Anti-FXIII (b) (4) positive Titer 2.3

Source: IND 10674 amend 49 MEDWATCH; STN125398 Listing 14.3.4.8: Listing of Positive Laboratory Test Results : Immunology - Antibody specific -Full Analysis Set p. 355 of 705

Subject ID: (b) (6) 8 y.o. male [Spain]

Date	Event
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4/15/2009	First Dose
5/14/2009	Second Dose
6/11/2009	Anti-FXIII (b) (4) positive Titer 2.3 (result not known unit 7/21/2009); Third dose (visit 5)
7/9/2009	Anti-FXIII (b) (4) positive Titer 2.3; neutralizing Ab test negative
8/5/2009	Blood sample drawn;
8/7/2009	Testing lab reported results of 8/5/2009 blood sample: Anti-FXIII (b) (4) positive Titer 2.0; Fourth Dose
9/3/2009	“On 03-SEP-2009 the patient recovered from the event. Anti RFactor XIII antibody: AB Tier 1 RR. Anti RFactor XIII AB Tier 2: AB Tier2: NAS”; Fifth Dose
10/01/2009	Sixth Dose
10/29/2009	Seventh Dose
11/26/2009	Eighth Dose
12/22/2009	Ninth Dose
1/19/2009	Tenth Dose
2/18/2010	Eleventh Dose
3/18/2010	Twelfth Dose

Source: STN125398

Subject ID: (b) (6) 8 y.o. male [Canada]

Date	Event
3/3/2009	Neg for anti-FXIII antibodies
4/2/2009	First Dose
4/16/2009	Anti-FXIII (b) (4) positive Titer 2.6; “on that day he still showed a good FXIII level”
4/29/2009	Anti-FXIII (b) (4) negative but re-tested Anti-FXIII (b) (4) positive Titer 2.0 and antibody specific (AS); received second dose rFXIII with “good recovery”;
5/27/2009	Third and last dose rFXIII; Clot solubility test: No lysis Anti recombinant factor XIII antibody (b) (4) result: NAS (Non-antibody specific) A2B2 (b) (4) Pending ug/ml (7.5 - 22.9) B-subunit (b) (4) Pending ug/ml (2.23 - 6.64) A2, (b) (4) Pending ug/ml (3.6 - 10.6) Factor XIII activity Berichrom: 0.298 IU/ml (0.32 - 1.52) Inh AB (not detectable): NO
6/24/2009	“The study's safety committee met on 24-JUN-2009 and decided to let the patient continue in the trial for the following reasons: <ul style="list-style-type: none"> – the antibodies observed after first dose of rFXIII were observed at a low titer – following re-administration of rFXIII the specific anti-FXIII antibodies could not be detected anymore – two patients have previously developed low titer antibodies against rFXIII. Following change of treatment to alternative

	FXIII treatment, no increase in antibodies were observed, i.e. a rescue treatment is available – - all antibodies were non-neutralising”
6/25/2009	Family decides to withdraw subject

Source: IND 10674 amend 56 MEDWATCH

6.1.12.6 Clinical Test Results

The F13CD-1725 study population consisted of otherwise healthy FXIII congenitally-deficient subjects undergoing routine prophylaxis with rFXIII_{A2}. Appendix 4 offers a broad overview of the health of these subjects by comparing platelet count, fibrinogen levels, and red blood cell (RBC) counts during the course of the study.

6.1.12.7 Dropouts and/or Discontinuations

Subject	Reason for Withdrawal	Initiator of Withdrawal	Comment
(b) (6)	Positive antibody results	Investigator	Withdrawn from treatment (only)
	Withdrawal criteria	Sponsor	
	AE	Investigator	
	Other	Subject	Personal reasons
	Withdrawal criteria (pregnancy)	Investigator	
	Positive antibody results	Investigator	Withdrawn from treatment (only)
	Positive antibody results	Investigator	Withdrawn from treatment (only)

(b) (6)	Other	Legal Authorized Representative	Parents and subject wanted to withdraw due to too many blood draws
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Source: STN125398/OS F13CD-1725 Clinical Trial Report, 16.2.1.2: Listing of Withdrawn Subjects

6.2.3 Population

The original protocol for F13CD-3720 only allowed enrollment of subjects who had completed F13CD-1725, in which case the first dose was on “visit 1”; however, in September 2010 Novo Nordisk amended F13CD-3720 to permit enrollment of subject who had not been enrolled into F13CD-1725, in which case the first dose was on “visit 1-day 28” to permit analysis of baseline test results.

6.2.4 Study Treatments or Agents Mandated by the Protocol

From the final protocol for F13CD-3720 as amended September 2010:

For subjects who completed F13CD-1725 the trial starts with a combined screening, dosing, and assessment, visit (Visit 1). Visit 1 must occur on the same day as the EOT visit in F13CD-1725 trial. After visit 1, the subject will attend the clinic for dosing, and assessments/blood sampling, every month. During the trial, a dosing schedule of trial product administration every 28 days (+/-2 days) will be maintained. Assessment visits will be performed at 12 week intervals with two interim visits being completed in between the assessment visits at day 28 and day 56 (e.g. visit 1; visit 1 day 28; visit 1 day 56; visit 2; visit 2 day 28; visit 2 day 56; visit 3 etc.). Telephone or email contacts with the subject must be maintained between the visits to the clinic (section 8.1.6).

For all other subjects visit 1 is defined as the screening visit (no dosing with rFXIII). The first dosing with rFXIII will take place at “Visit 1 day 28” if the subject’s subunit A-deficiency is confirmed by genotyping. Hereafter, a dosing schedule of trial product administration every 28 days (+/-2 days) will be maintained, as well as telephone or email contacts between the visits to the clinic (section 8.1.6).

During the treatment period, any need for additional FXIII administration as per Investigator judgment for treatment of acute bleeding episodes (breakthrough bleedings) must be covered by the administration of local standard practice with FXIII containing products. The subject will be requested to return to the clinic in case a treatment-requiring bleeding episode occurs for an unscheduled visit (section 8.1.5).

The assessments and local laboratory results will be recorded in the CRF. Central laboratory results will not be recorded in the CRF (section 8.4.1).

In case a subject is being prematurely withdrawn from the trial the Investigator will ensure that the procedures for the end of trial visit are undertaken, if possible (section 8.1.4). The primary reason (Adverse Event, non-compliance with protocol or other) for discontinuation must be specified in the CRF. Even if the subject is not able to attend the end of trial visit, the end of trial form and the drug accountability form must be completed.

6.2.5 Directions for Use

6.2.6 Sites and Centers

6.2.7 Surveillance/Monitoring

6.2.8 Endpoints and Criteria for Study Success

6.2.9 Statistical Considerations & Statistical Analysis Plan

6.2.10 Study Population and Disposition

Up to and including the cut-off date for data included in this preliminary report (30 November 2010) only patients participating in Trial F13CD-1725 were enrolled in Trial F13CD-3720.

Table 10–1 Subject Disposition

	(b) (4)	Novo Nordisk	Total
	rFXIII 35 IU/Kg N (%)	rFXIII 35 IU/Kg N (%)	rFXIII 35 IU/Kg N (%)
Randomised	26	31	33
Exposed	26 (100.0)	31 (100.0)	33 (100.0)
Withdrawn from Trial Other Reason	1 (3.8)	1 (3.2)	2 (6.1)
Withdrawal Criteria	1 (3.8)	0 (0.0)	1 (3.0)
Full Analysis Set	26 (100.0)	31 (100.0)	33 (100.0)
Safety Analysis Set	26 (100.0)	31 (100.0)	33 (100.0)

N: Number of subjects

%: Proportion of exposed subjects

Source: Original sBLA 125398; Clinical Study Report F13CD-3720, p.36 of 380

6.2.10.1 Populations Enrolled/Analyzed

6.2.10.1.1 Demographics

Table 11–1 Baseline Demographics - Full Analysis Set

	(b) (4)	Novo Nordisk	Total
	rFXIII 35 IU/Kg N (%)	rFXIII 35 IU/Kg N (%)	rFXIII 35 IU/Kg N (%)

Number of Subjects	26	31	33
Age (years)			
N	26	31	33
Mean (SD)	29.7 (15.6)	29.0 (16.9)	28.8 (16.4)
Median	25.0	25.0	25.0
Min ; Max	8.0 ; 57.0	7.0 ; 60.0	7.0 ; 60.0
Sex, N(%)			
N	26 (100)	31 (100)	33 (100)
Female	11 (42)	11 (35)	13 (39)
Male	15 (58)	20 (65)	20 (61)
Race, N(%)			
N	26 (100)	31 (100)	33 (100)
Black or African American	0 (0)	2 (6)	2 (6)
White	18 (69)	22 (71)	23 (70)
Unknown	1 (4)	1 (3)	1 (3)
Asian	3 (12)	2 (6)	3 (9)
Other	4 (15)	4 (13)	4 (12)

The French patients are marked as Unknown as per the French Authorities Guidelines

SD: standard deviation

Source: Original sBLA 125398; Clinical Study Report F13CD-3720, p.37 of 380

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

6.2.10.1.3 Subject Disposition

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

6.2.11.2 Analyses of Secondary Endpoints

6.2.11.3 Subpopulation Analyses

6.2.11.4 Dropouts and/or Discontinuations

6.2.11.5 Exploratory and Post Hoc Analyses

6.2.12 Safety Analyses

6.2.12.1 Methods

The demographics of the safety population for study F13CD-3720 is described in section 6.2.10.1.1.

6.2.12.2 Overview of Adverse Events

All reported treatment-emergent adverse events (TEAEs) for study F13CD-3720 are given in **Appendix 4**, where they are classified as nonserious or serious, and by severity.

6.2.12.3 Deaths

No deaths occurred during the trial.

6.2.12.4 Nonfatal Serious Adverse Events

Table 12–4 Listing of Treatment-emergent Serious Adverse Events by Subjects – Full Analysis Set

Subject ID	Age	Preferred term	Severity	Days since dosing	Relationship	Outcome
(b) (6)	12	Skin laceration	SEVERE	24	UNLIKELY	RECOVERED
(b) (6)	55	Carpal tunnel syndrome	MODERATE	17	UNLIKELY	RECOVERED

Source: Original sBLA 125398; Clinical Study Report F13CD-3720, p.46 of 380

6.2.12.5 Adverse Events of Special Interest (AESI)

6.2.12.6 Clinical Test Results

6.2.12.7 Dropouts and/or Discontinuations

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

7.1.1 Methods of Integration

7.1.2 Demographics and Baseline Characteristics

7.1.3 Subject Disposition

7.1.4 Analysis of Primary Endpoint(s)

7.1.5 Analysis of Secondary Endpoint(s)

7.1.6 Other Endpoints

7.1.7 Subpopulations

7.1.8 Persistence of Efficacy

7.1.9 Product-Product Interactions

7.1.10 Additional Efficacy Issues/Analyses

7.1.11 Efficacy Conclusions

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

8.2.3 Categorization of Adverse Events

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

8.4 Safety Results

8.4.1 Deaths

8.4.2 Nonfatal Serious Adverse Events

8.4.3 Study Dropouts/Discontinuations

8.4.4 Common Adverse Events

8.4.5 Clinical Test Results

8.4.6 Systemic Adverse Events

8.4.7 Local Reactogenicity

8.4.8 Adverse Events of Special Interest

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

8.5.2 Time Dependency for Adverse Events

8.5.3 Product-Demographic Interactions

8.5.4 Product-Disease Interactions

8.5.5 Product-Product Interactions

8.5.6 Human Carcinogenicity

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

8.5.8 Immunogenicity (Safety)

8.5.9 Person-to-Person Transmission, Shedding

8.6 Safety Conclusions

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

9.1.2 Use During Lactation

9.1.3 Pediatric Use and PREA Considerations

9.1.4 Immunocompromised Patients

9.1.5 Geriatric Use

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

10. CONCLUSIONS

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

11.2 Risk-Benefit Summary and Assessment

The submission includes a Risk Management plan consisting of two parts: 1) established and planned procedures to deal with risks, and 2) evaluation of the need for, and the risk minimization plan.

The follow table is taken from the submitted Risk Management Plan, and it summarizes proposed actions to address identified risks:

Table 43 Proposed RMP

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Identified Risks		
Non-neutralising antibodies	<ul style="list-style-type: none"> • Continued analysis of safety data • Structured follow-up form and expanded reporting • Offering analysis of blood samples when formation of antibodies is suspected • The labelling describes that frequency of non-neutralising antibodies is common ($\geq 1/100$ to $<1/10$), based on exposure in 50 patients. 	Not applicable
Important Potential Risks		
Neutralising antibodies	<ul style="list-style-type: none"> • Continued analysis of safety data • Structured follow-up form and expanded reporting • Collection and continued analysis of safety information via the post-marketing observational study • Offering testing when formation of antibodies is suspected • The labelling describes: “Inhibitor formation to rFXIII therapy has not been detected in clinical trials. Inhibitors may be suspected in the event of lack of therapeutic response observed as clinical bleeding or demonstrated by laboratory findings including FXIII activities that fail to reach expected levels. In the event that inhibitors are suspected analysis for antibodies should be performed.” 	Not applicable
Allergic reactions	<ul style="list-style-type: none"> • Continued analysis of safety data • Structured follow-up form • Collection and continued analysis of safety information via the post-marketing observational study • The labelling describes: “As rFXIII is a recombinant protein it may cause allergic reactions including anaphylactic reaction. An anaphylactic reaction has been seen following the administration of rFXIII in 1 patient in a clinical trial investigating the use of rFXIII following cardiac surgery. The patient also received a concomitant medication that is known to have a risk of anaphylactic reaction.” 	Not applicable

Thrombo embolic events	<ul style="list-style-type: none"> • Continued analysis of safety data • Structured follow-up form • Collection and continued analysis of safety information via the post-marketing observational study • The labelling describes: <ul style="list-style-type: none"> – “In case of predisposition to conditions of thrombosis, caution should be exercised due to the fibrin-stabilising effect of rFXIII. A stabilisation of the thrombus might occur, resulting in increased risk of vessel occlusions.” – “Incorrect storage of the product after reconstitution must be avoided as it may result in loss of sterility and in increased levels of nonproteolytical activated rFXIII. Increased levels of non-proteolytical activated rFXIII may increase the risk of thrombosis.” 	Voluntary educational material is being prepared to decrease the risk of toxicity in connection with incorrect storage (draft in Annex 10).
Lack of efficacy	<ul style="list-style-type: none"> • Continued analysis of safety data • Collection and continued analysis of safety information via the post-marketing observational study • The labelling describes: “Patients with hepatic impairment have not been studied. rFXIII may not be effective in patients with hepatic impairment due to decreased levels of FXIII B-subunits.” 	Not applicable
Important Missing Information		
Children (<6 years of age)	<ul style="list-style-type: none"> • Continued analysis of safety data (F13CD-3760, F13CD-3835, NN1841-3868). • Collection and continued analysis of safety information via the post-marketing observational study. 	Not applicable
Elderly	<ul style="list-style-type: none"> • Continued analysis of safety data • Collection and continued analysis of safety information via the post-marketing observational study. 	Not applicable
Pregnant and lactating women	<ul style="list-style-type: none"> • Collect exposure and follow-up on outcome in observational studies and post-marketing • Collection and continued analysis of safety information via the post-marketing observational study • The labelling describes: “rFXIII should be avoided during pregnancy unless the benefits clearly outweigh the risks.” 	Not applicable
Other Safety Concerns		
Potential off-label use	<ul style="list-style-type: none"> • The labeling describes: “The on-demand treatment of acute bleeds or breakthrough bleeds with rFXIII has not been studied in clinical trials. Treatment should be initiated under the supervision of a doctor experienced in the treatment of rare bleeding disorders.” • Training in SOPs concerning off-label information. 	Not applicable

11.3 Discussion of Regulatory Options

11.4 Recommendations on Regulatory Actions

11.5 Labeling Review and Recommendations

11.6 Recommendations on Postmarketing Actions

-
-
-

3.

Appendix 1. Study F13CD-1725 Eligibility Criteria and Schedule of Events Flowchart

Eligibility Criteria

Inclusion Criteria

1. 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).
2. Diagnosis of congenital FXIII A-subunit deficiency (confirmed by genotyping at screening visit).
3. Treatment with regular FXIII replacement therapy initiated at least 6 months prior to screening and one of the following : a documented history of ≥ 1 treatment-requiring bleeding episode prior to initiation of regular replacement therapy or a documented family history of FXIII congenital deficiency (only for subjects on regular replacement therapy prior to screening).
4. Documented history of ≥ 2 bleeding episodes requiring treatment with FXIII containing blood products within the last 12 months prior to screening (only for subjects receiving on-demand treatment prior to screening).
5. Subjects with age ≥ 6 years and a weight ≥ 20 kg. Before enrolling subjects ≥ 6 to < 12 years of age in the EU countries, 7 subjects have to be exposed for 12 weeks (3 exposures) to trial product with a safe safety profile. (See section 12.7).
6. If female and of child-bearing potential: negative pregnancy test at screening.

Exclusion Criteria

1. Known neutralizing antibodies (inhibitors) towards FXIII.
2. Any known congenital or acquired coagulation disorder other than congenital FXIII deficiency.
3. Documented history of ≥ 2 treatment-requiring bleeding episodes per year during previous regular replacement therapy with FXIII containing blood products (FFP, pd FXIII and cryoprecipitate).
4. Platelet count (thrombocytes) $< 75 \times 10^9/L$.
5. Known or suspected allergy to trial product(s) or related products.
6. Previous participation in this trial.
7. Subject has received treatment with any investigational drug within 30 days of trial enrolment, except pdFXIII.
8. Planned major surgery during the trial period. Catheter, ports and dental extractions do not count as surgeries and will not exclude the subject.
9. Renal insufficiency defined as current dialysis therapy.
10. Any history of confirmed venous or arterial thrombo-embolic events.
11. Subject has received any anti-thrombotic or anti-platelet drugs within 7 days of trial enrollment.
12. Subject has medical, social or psychosocial factors expected to impact compliance or safety.
13. 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.

14. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation in participating in the trial.
15. Females of childbearing potential who are pregnant, breastfeeding or intend to become pregnant or are not using adequate contraceptive methods (adequate contraceptive measures as required by local law or practice) from the time of enrollment to completion of all follow-up trial visits.

Schedule of Events Flowchart

Trial Period	Screening	Treatment Period with rFXIII Replacement Therapy every 4th Week														EOT ⁶	Unscheduled Visit
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	
Time & Visit Windows	Wk -4 ± 2 days	Wk 0	Wk 2 ± 2 days	Wk 4 ± 2 days	Wk 8 ± 2 days	Wk 12 ± 2 days	Wk 16 ± 2 days	Wk 20 ± 2 days	Wk 24 ± 2 days	Wk 28 ± 2 days	Wk 32 ± 2 days	Wk 36 ± 2 days	Wk 40 ± 2 days	Wk 44 ± 2 days	Wk 48 ± 2 days	Wk 52 ± 2 days	In case of treatment-requiring bleeding
Informed Consent	•																
Inclusion / Exclusion Criteria	•	•															
Withdrawal Criteria		•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Demographic Data	•																
Diagnosis and type of Congenital FXIII Deficiency	•																
Medical History / Concomitant Illness	•																
Concomitant Medication	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Physical Examination	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Body Measurements	•	• ¹		• ¹		• ¹											
Vital Signs (Blood	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Trial Period	Screening	Treatment Period with rFXIII Replacement Therapy every 4th Week														EOT ⁶	Unscheduled Visit
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	
Time & Visit Windows	Wk -4 ± 2 days	Wk 0	Wk 2 ± 2 days	Wk 4 ± 2 days	Wk 8 ± 2 days	Wk 12 ± 2 days	Wk 16 ± 2 days	Wk 20 ± 2 days	Wk 24 ± 2 days	Wk 28 ± 2 days	Wk 32 ± 2 days	Wk 36 ± 2 days	Wk 40 ± 2 days	Wk 44 ± 2 days	Wk 48 ± 2 days	Wk 52 ± 2 days	In case of treatment-requiring bleeding
Pressure / Pulse)																	
Telephone Contact				• ²	• ²												
Dosage Calculation		•		•	•	•	•	•	•	•	•	•	•	•	•	•	
rFXIII Administration & Drug Accountability		•		•	•	•	•	•	•	•	•	•	•	•	•	•	
Previous Treatment Regime with FXIII Containing Products	•																
Bleeding History	•																
Treatment of Acute Bleedings																	•
Bleeding Episode Details		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Hospitalisation Days		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Emergency Room Visits		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Trial Period	Screening	Treatment Period with rFXIII Replacement Therapy every 4th Week														EOT ⁶	Unscheduled Visit
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	
Time & Visit Windows	Wk -4 ± 2 days	Wk 0	Wk 2 ± 2 days	Wk 4 ± 2 days	Wk 8 ± 2 days	Wk 12 ± 2 days	Wk 16 ± 2 days	Wk 20 ± 2 days	Wk 24 ± 2 days	Wk 28 ± 2 days	Wk 32 ± 2 days	Wk 36 ± 2 days	Wk 40 ± 2 days	Wk 44 ± 2 days	Wk 48 ± 2 days	Wk 52 ± 2 days	In case of treatment-requiring bleeding
Hematology (local lab)	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Biochemistry (local lab)	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Urinalysis (local lab)	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
FXIII Lab Parameters (central lab)	•	• ⁴	•	• ⁴	• ³												
Genotyping (central lab)	•																
Immunology (central lab)	•	• ³	• ³	• ³	• ³	• ³	• ³	• ³	• ³	• ³	• ³	• ³	• ³	• ³	• ³	• ³	• ³
Coagulation Parameters (central lab)	•	• ⁴	•	• ⁴	• ³												
Clot Solubility Test (local lab)	•	• ⁴	•	• ⁴	• ³												
Pregnancy Test (local lab)	•				• ⁵												

Trial Period	Screening	Treatment Period with rFXIII Replacement Therapy every 4th Week														EOT ⁶	Unscheduled Visit
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	
Time & Visit Windows	Wk -4 ± 2 days	Wk 0	Wk 2 ± 2 days	Wk 4 ± 2 days	Wk 8 ± 2 days	Wk 12 ± 2 days	Wk 16 ± 2 days	Wk 20 ± 2 days	Wk 24 ± 2 days	Wk 28 ± 2 days	Wk 32 ± 2 days	Wk 36 ± 2 days	Wk 40 ± 2 days	Wk 44 ± 2 days	Wk 48 ± 2 days	Wk 52 ± 2 days	In case of treatment-requiring bleeding
Biomarkers		● ⁴		● ⁴		● ⁴		● ⁴		● ⁴		● ⁴		● ⁴			
Adverse Events / Serious Adverse Events	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
End of Trial Form																●	

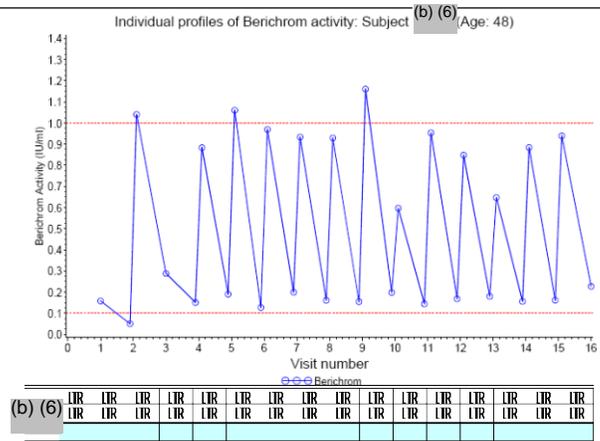
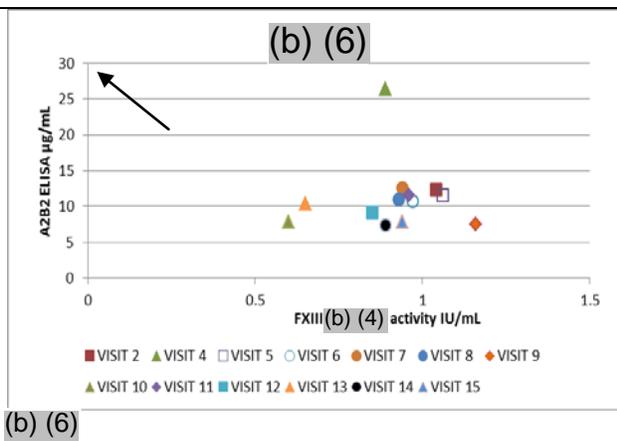
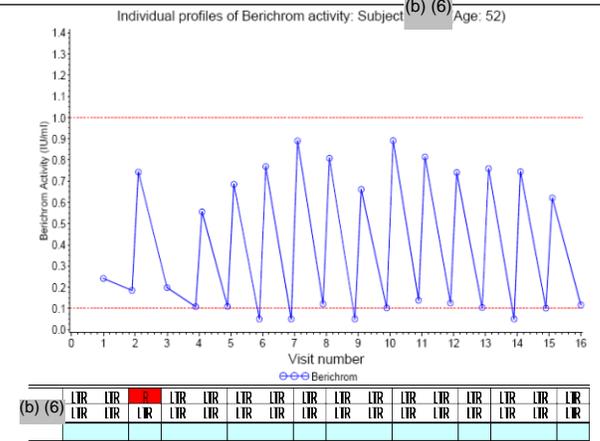
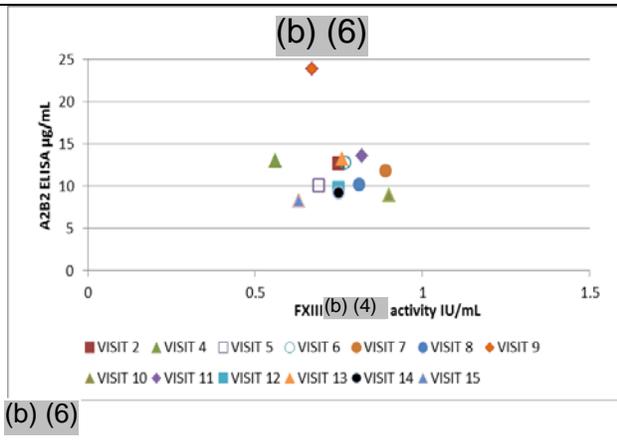
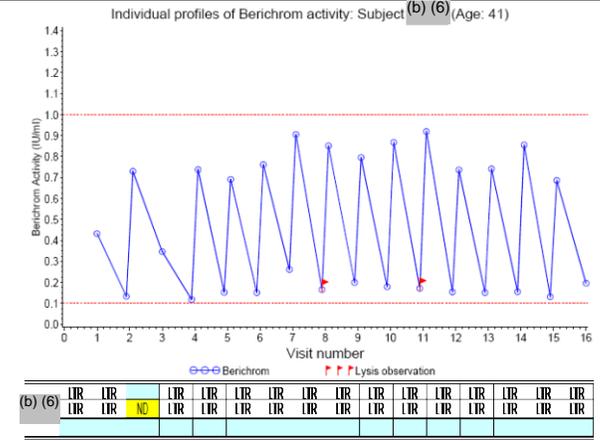
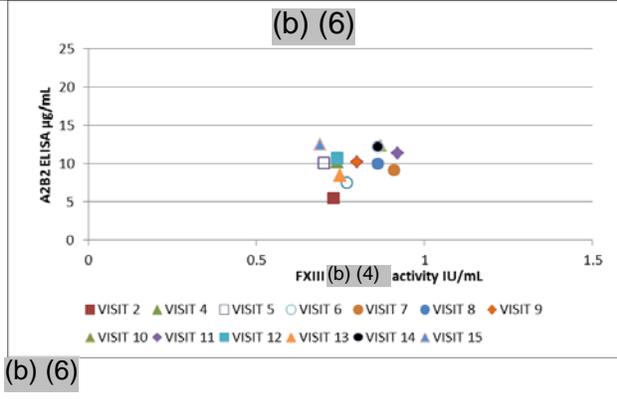
- ¹ Only body weight;
- ² Telephone contact to be made 14 days ± 3 days after each clinic visit
- ³ Samples must be obtained before any FXIII containing product is administered;
- ⁴ Sampling to be performed before rFXIII dosing and 1 hour after;
- ⁵ For women of child-bearing potential: Pregnancy test only to be repeated if the last test is ≥ 3 months ago or if a menstrual period is missed;
- ⁶ Early termination: EOT to be performed.

1 Hour Post Dose A₂B₂ µg/mL vs. FXIII Berichrom Activity by Study Visit

Pre-Post Dose FXIII with Efficacy and Antibody data

▶ Lysis observation
 ★★★ Bleeding
 —●— Berichrom
 ●●● Pos. antibody

LTR	Less Than Reportable in Tier 1	RR	Repeat Reactive in Tier 1	NAS	Not Antigen-Specific in Tier 2	AS	Antigen Specific in Tier 2
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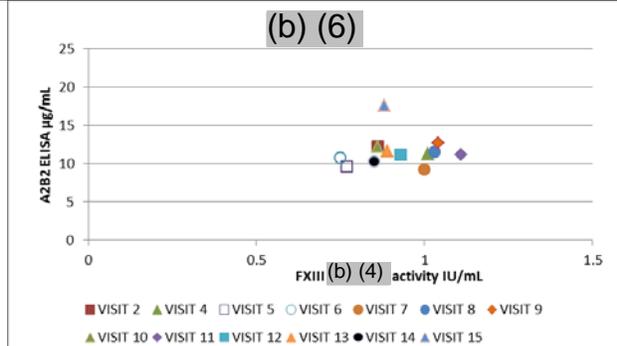


1 Hour Post Dose A₂B₂ µg/mL vs. FXIII Berichrom Activity by Study Visit

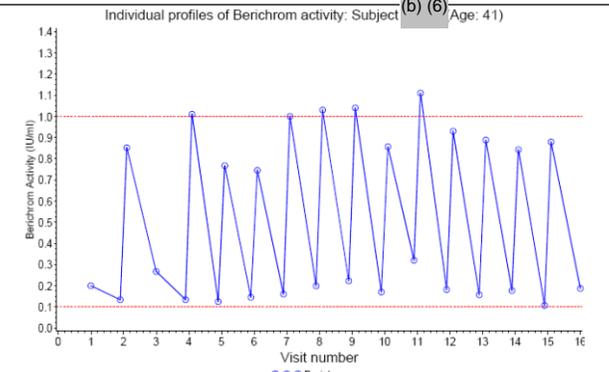
Pre-Post Dose FXIII with Efficacy and Antibody data

▶ Lysis observation
 ★ ★ ★ Bleeding
 —●— Berichrom
 ● ● ● Pos. antibody

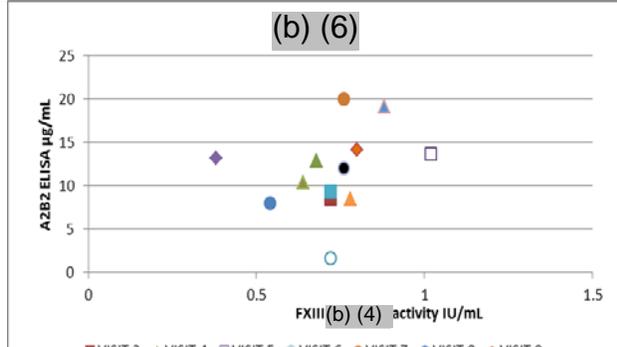
LTR	Less Than Reportable in Tier 1	RR	Repeat Reactive in Tier 1	RR	Reactive in Tier 1	NAS	Not Antigen-Specific in Tier 2	AS	Antigen Specific in Tier 2
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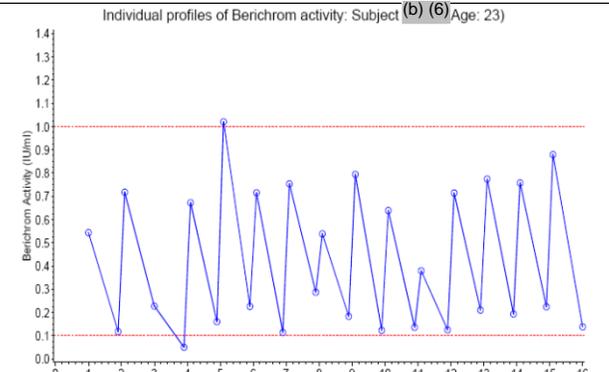
(b) (6)



(b) (6)	LTR																		
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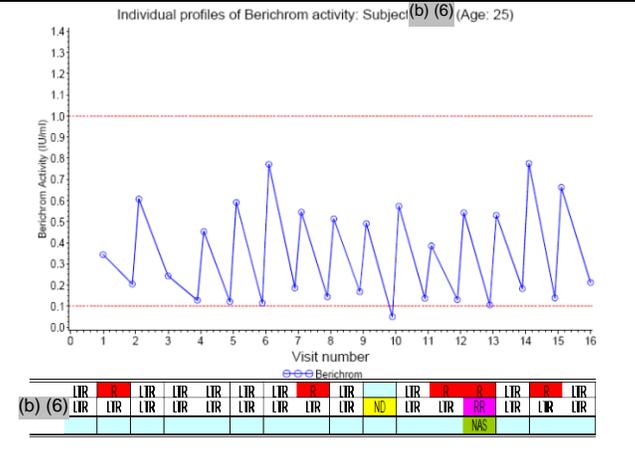
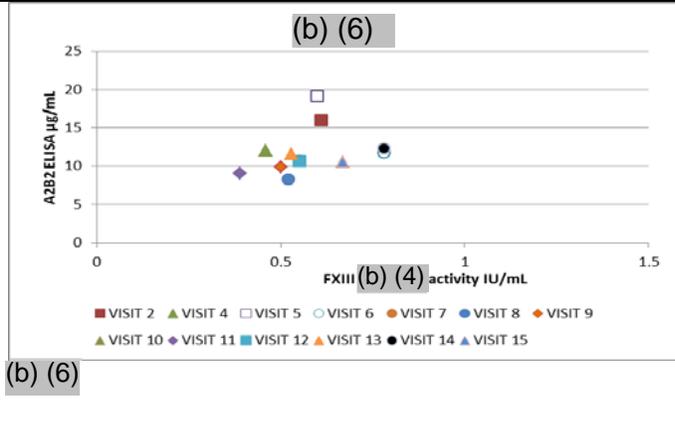
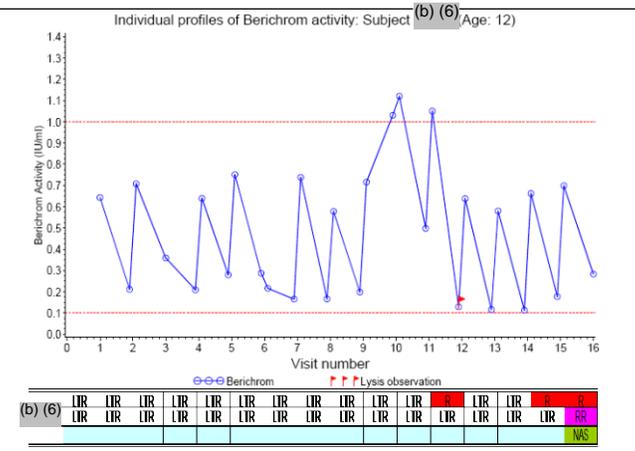
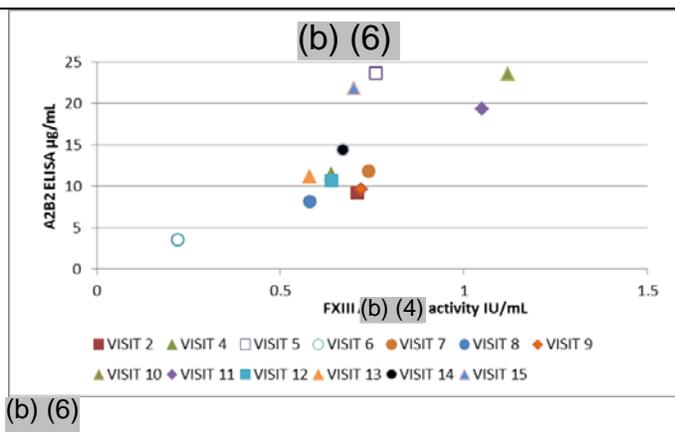
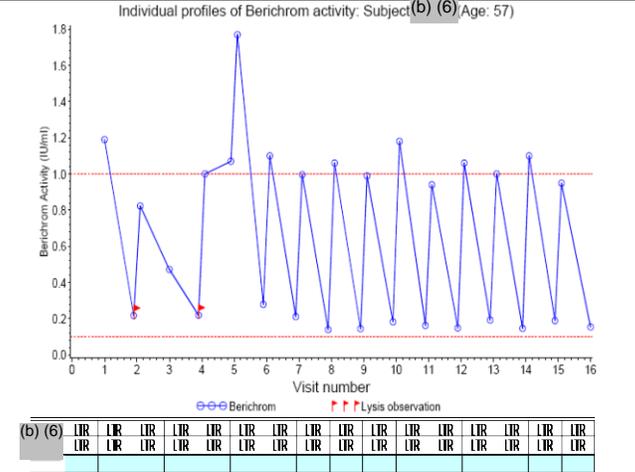
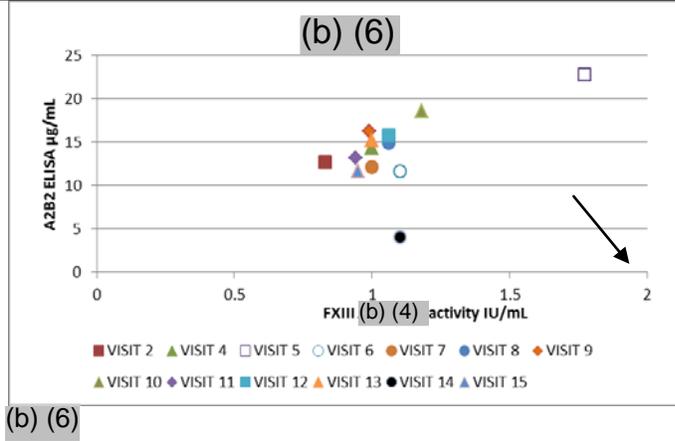


(b) (6)	LTR																		
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1 Hour Post Dose A₂B₂ µg/mL vs. FXIII Berichrom Activity by Study Visit

Pre-Post Dose FXIII with Efficacy and Antibody data

Lysis observation ★★★ Bleeding — Berichrom ●●● Pos. antibody
 LTR Less Than Reportable in Tier 1 R Reactive in Tier 1 RR Repeat Reactive in Tier 1 NAS Not Antigen-Specific in Tier 2 AS Antigen Specific in Tier 2

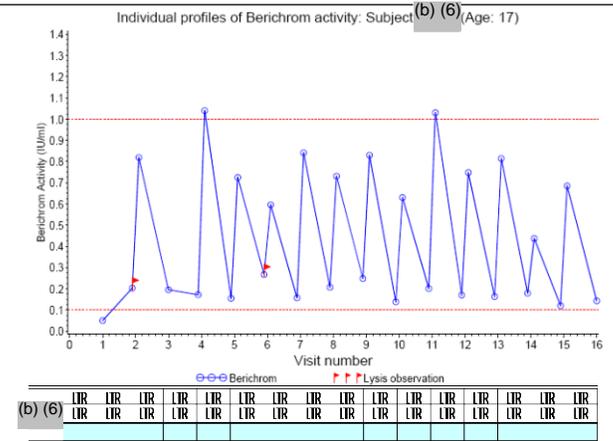
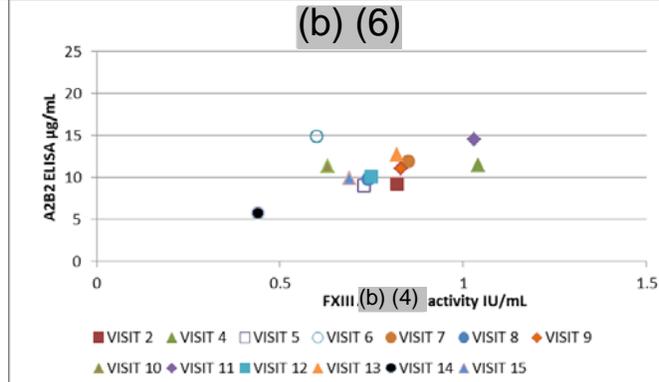


1 Hour Post Dose A₂B₂ µg/mL vs. FXIII Berichrom Activity by Study Visit

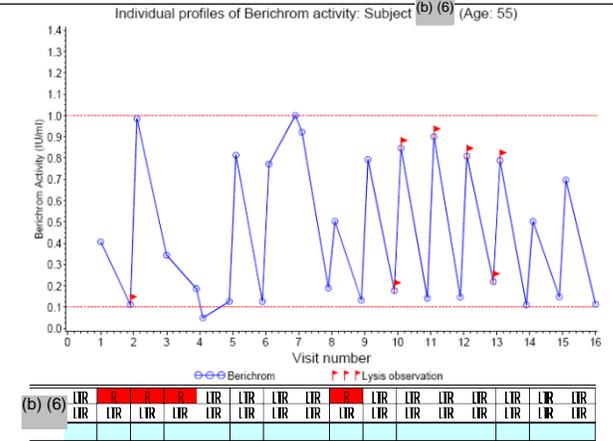
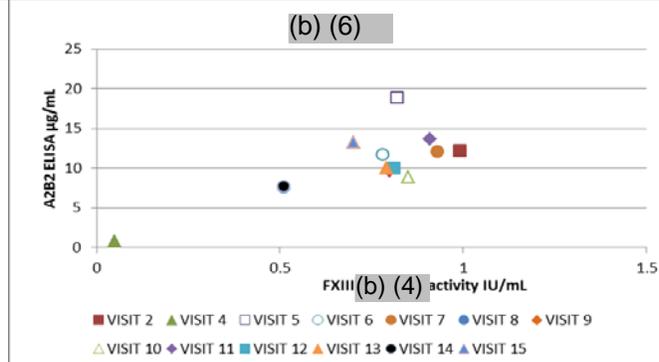
Pre-Post Dose FXIII with Efficacy and Antibody data

▶ Lysis observation
 ★★★ Bleeding
 —●— Berichrom
 ●●● Pos. antibody

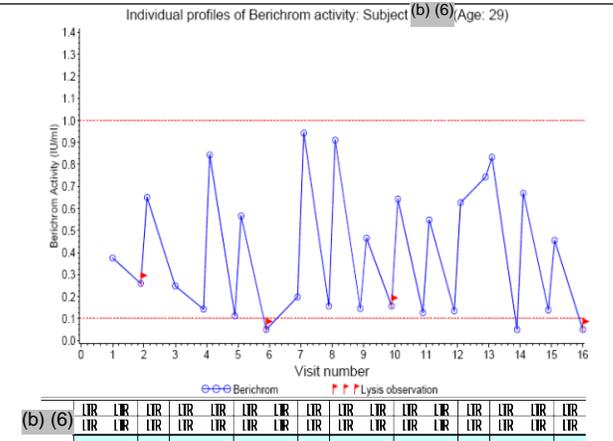
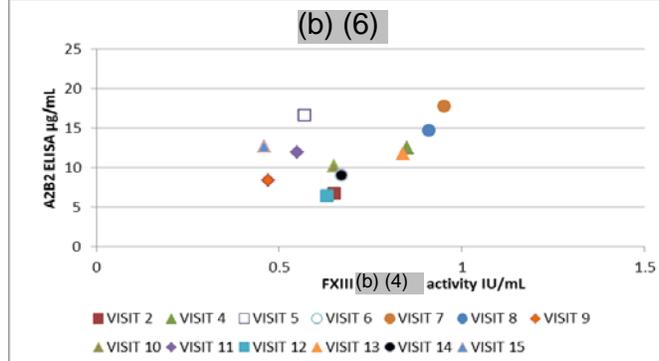
LTR	Less Than Reportable in Tier 1	RR	Reactive in Tier 1 Repeat Reactive in Tier 1	NAS	Not Antigen-Specific in Tier 2	AS	Antigen Specific in Tier 2
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(b) (6)



(b) (6) experienced “non-cardiac chest pain”, recovered



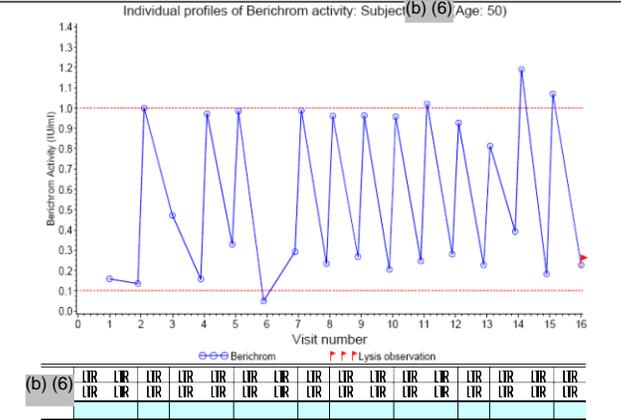
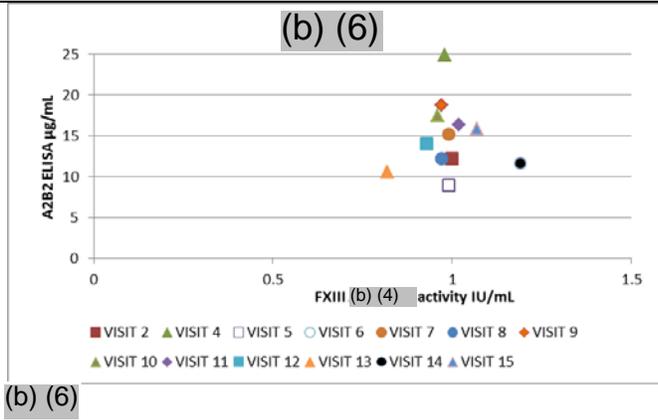
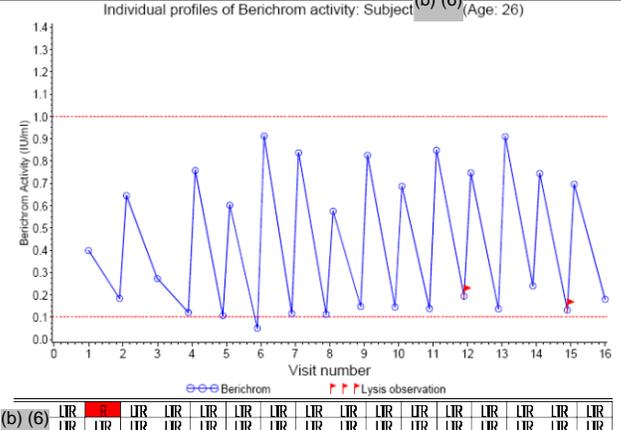
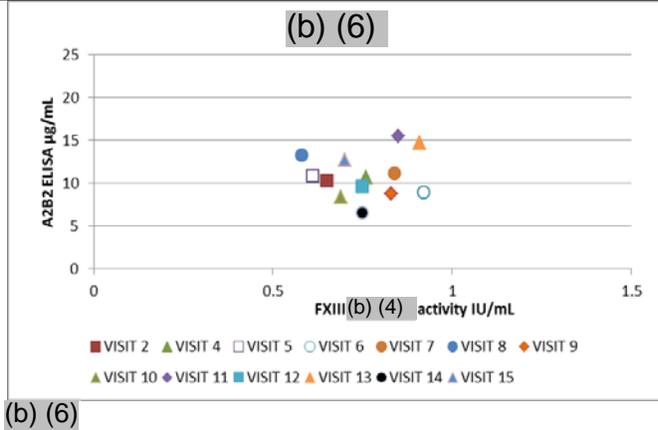
(b) (6)

1 Hour Post Dose A₂B₂ µg/mL vs. FXIII Berichrom Activity by Study Visit

Pre-Post Dose FXIII with Efficacy and Antibody data

▶ Lysis observation
 ★★★ Bleeding
 — Berichrom
 ●●● Pos. antibody

LTR	Less Than Reportable in Tier 1	RR	Repeat Reactive in Tier 1	RR	Reactive in Tier 1	NAS	Not Antigen-Specific in Tier 2	AS	Antigen Specific in Tier 2
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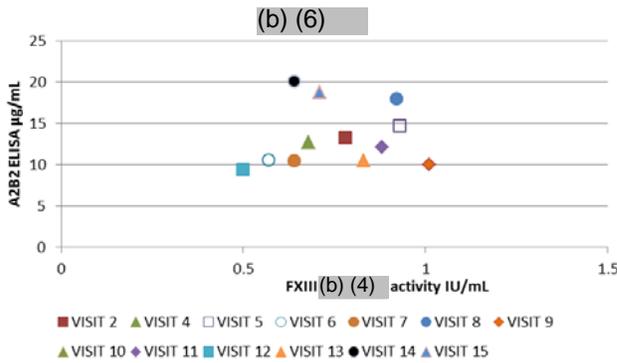


1 Hour Post Dose A₂B₂ µg/mL vs. FXIII Berichrom Activity by Study Visit

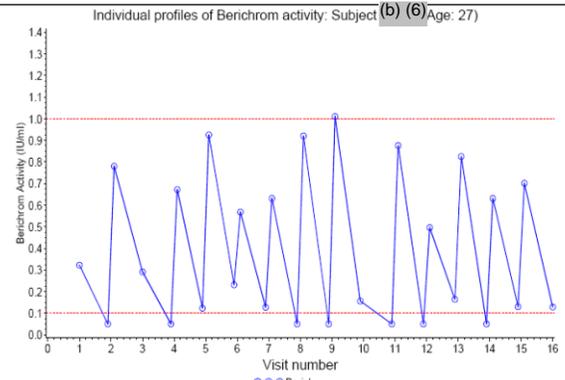
Pre-Post Dose FXIII with Efficacy and Antibody data

▶ Lysis observation
 ★ ★ ★ Bleeding
 —●— Berichrom
 ● ● ● Pos. antibody

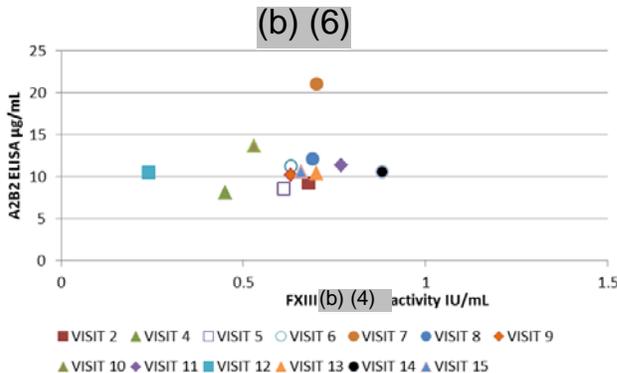
LTR	Less Than Reportable in Tier 1	R	Reactive in Tier 1	NAS	Not Antigen-Specific in Tier 2	AS	Antigen Specific in Tier 2
		RR	Repeat Reactive in Tier 1				



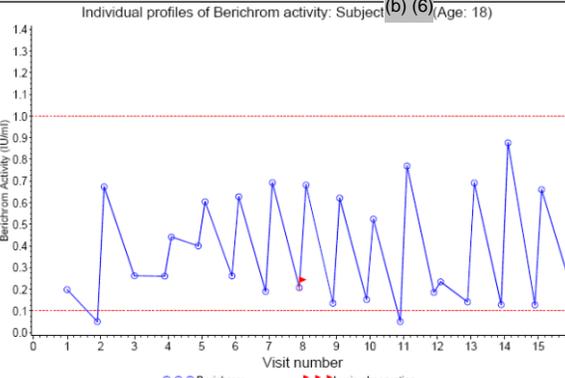
(b) (6)



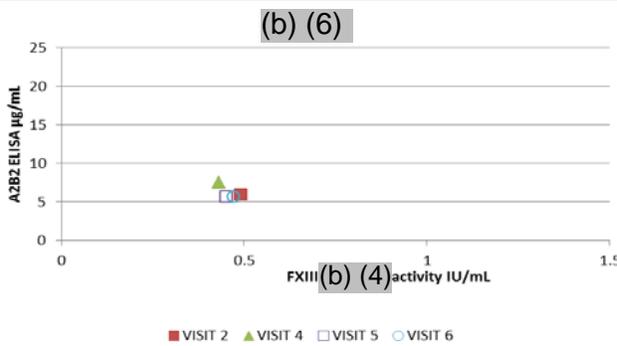
(b) (6)	LTR																		
	LTR																		



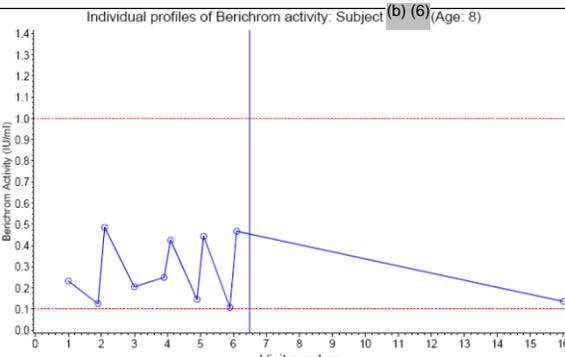
(b) (6)



(b) (6)	LTR																		
	LTR																		



(b) (6) withdrawn for adverse events “worsening leukopenia” and “worsening neutropenia”



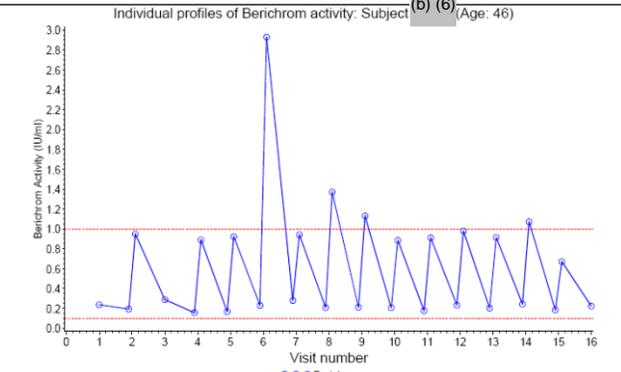
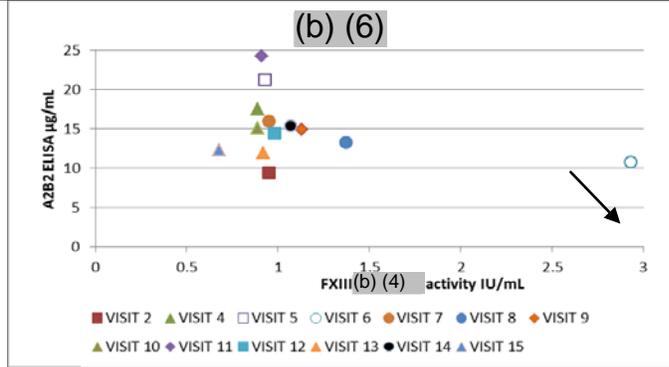
(b) (6)	LTR	R	LTR	LTR	LTR	R													LTR
	LTR	LTR	LTR	LTR	LTR	RR													LTR
							NAS												

1 Hour Post Dose A_2B_2 $\mu\text{g/mL}$ vs. FXIII Berichrom Activity by Study Visit

Pre-Post Dose FXIII with Efficacy and Antibody data

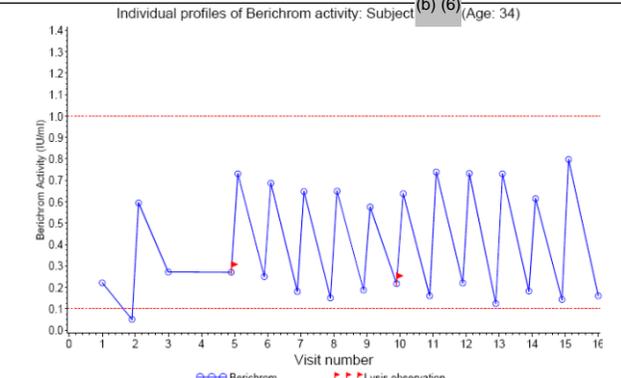
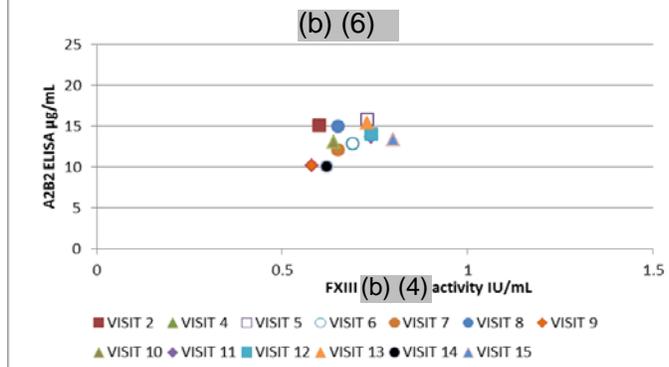
▶ Lysis observation
 ★★★ Bleeding
 — Berichrom
 ●● Pos. antibody

LTR	Less Than Reportable in Tier 1	RR	Repeat Reactive in Tier 1	NAS	Not Antigen-Specific in Tier 2	AS	Antigen Specific in Tier 2
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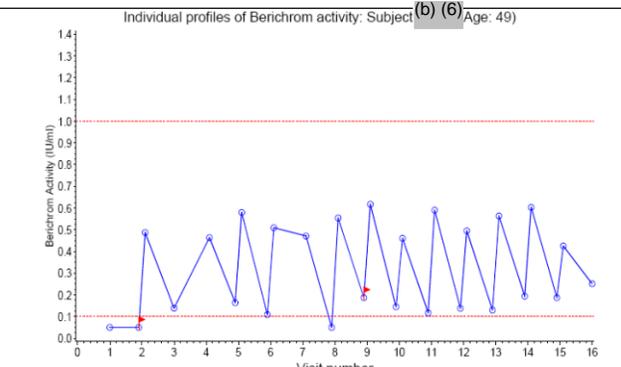
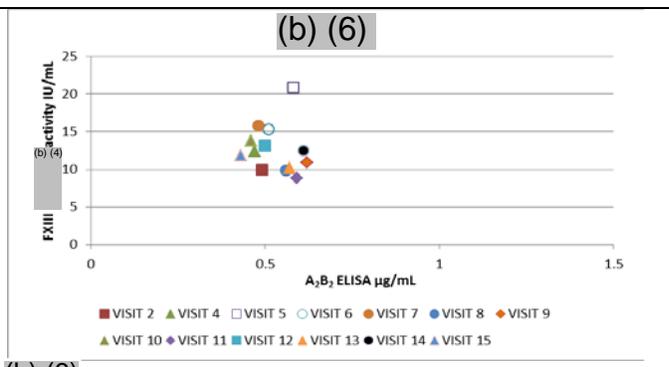
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(b) (6)



(b) (6)

(b) (6)



(b) (6)

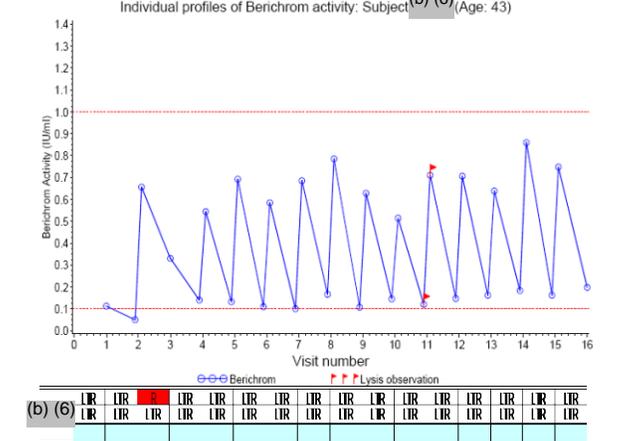
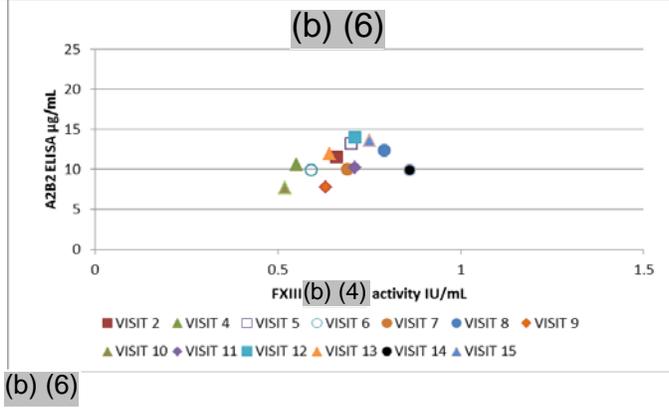
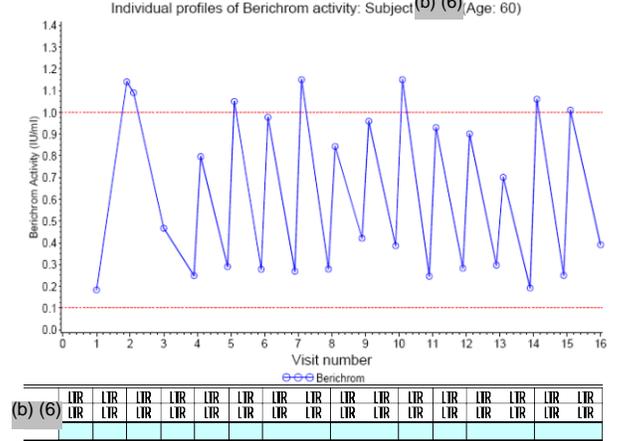
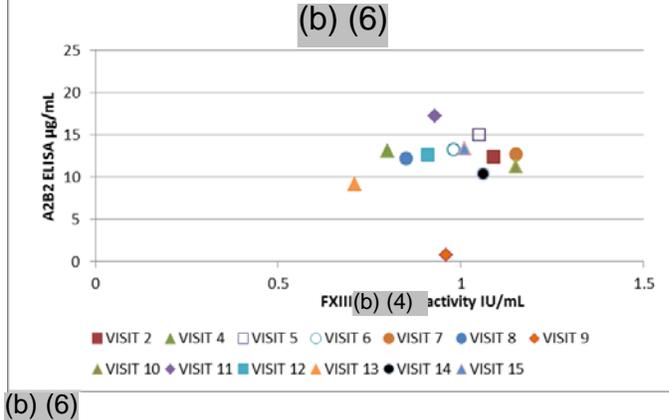
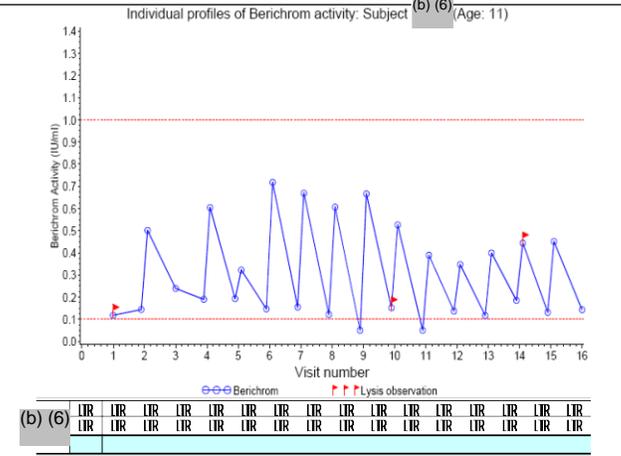
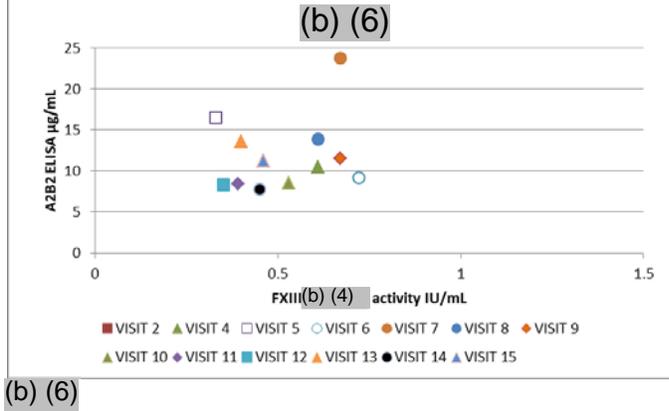
(b) (6)

1 Hour Post Dose A₂B₂ µg/mL vs. FXIII Berichrom Activity by Study Visit

Pre-Post Dose FXIII with Efficacy and Antibody data

▶ Lysis observation
 ★★★ Bleeding
 — Berichrom
 ●● Pos. antibody

LTR	Less Than Reportable in Tier 1	RR	Reactive in Tier 1 Repeat Reactive in Tier 1	NAS	Not Antigen-Specific in Tier 2	AS	Antigen Specific in Tier 2
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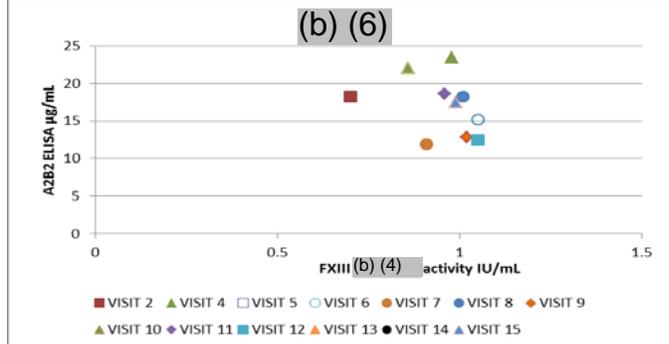


1 Hour Post Dose A₂B₂ µg/mL vs. FXIII Berichrom Activity by Study Visit

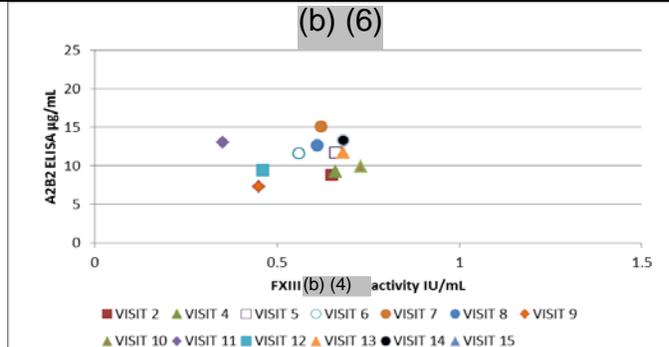
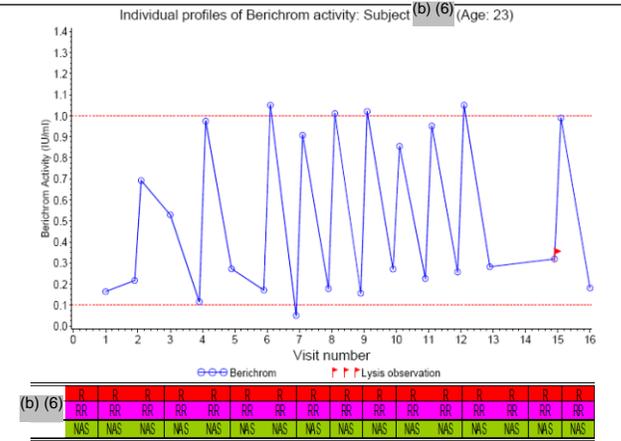
Pre-Post Dose FXIII with Efficacy and Antibody data

▶ Lysis observation
 ★★★ Bleeding
 — Berichrom
 ●● Pos. antibody

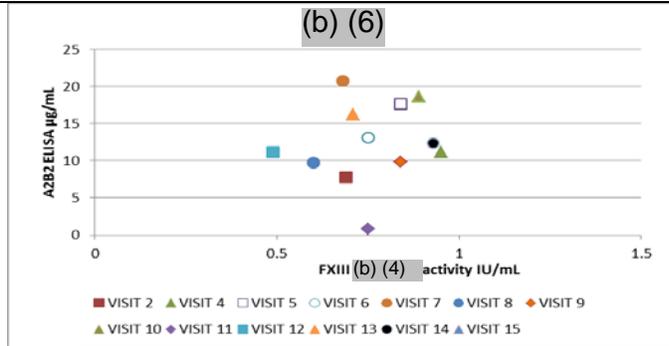
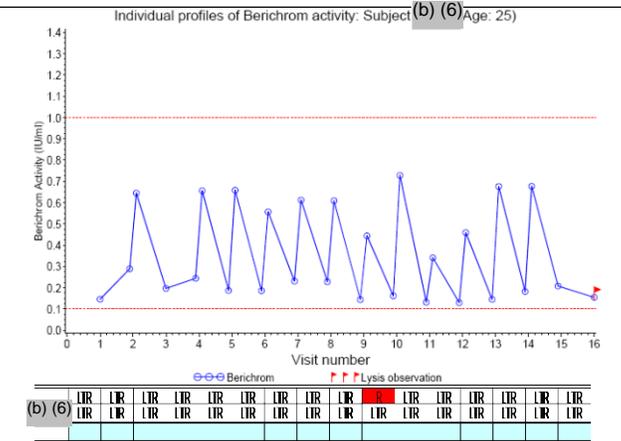
LTR	Less Than Reportable in Tier 1	R	Reactive in Tier 1	NAS	Not Antigen-Specific in Tier 2	AS	Antigen Specific in Tier 2
RR	Repeat Reactive in Tier 1						



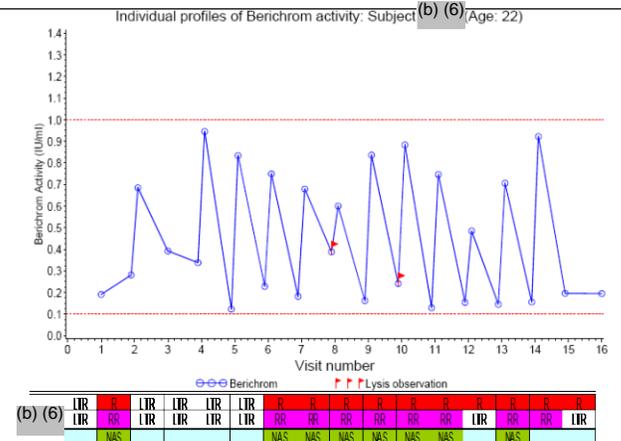
(b) (6)



(b) (6)



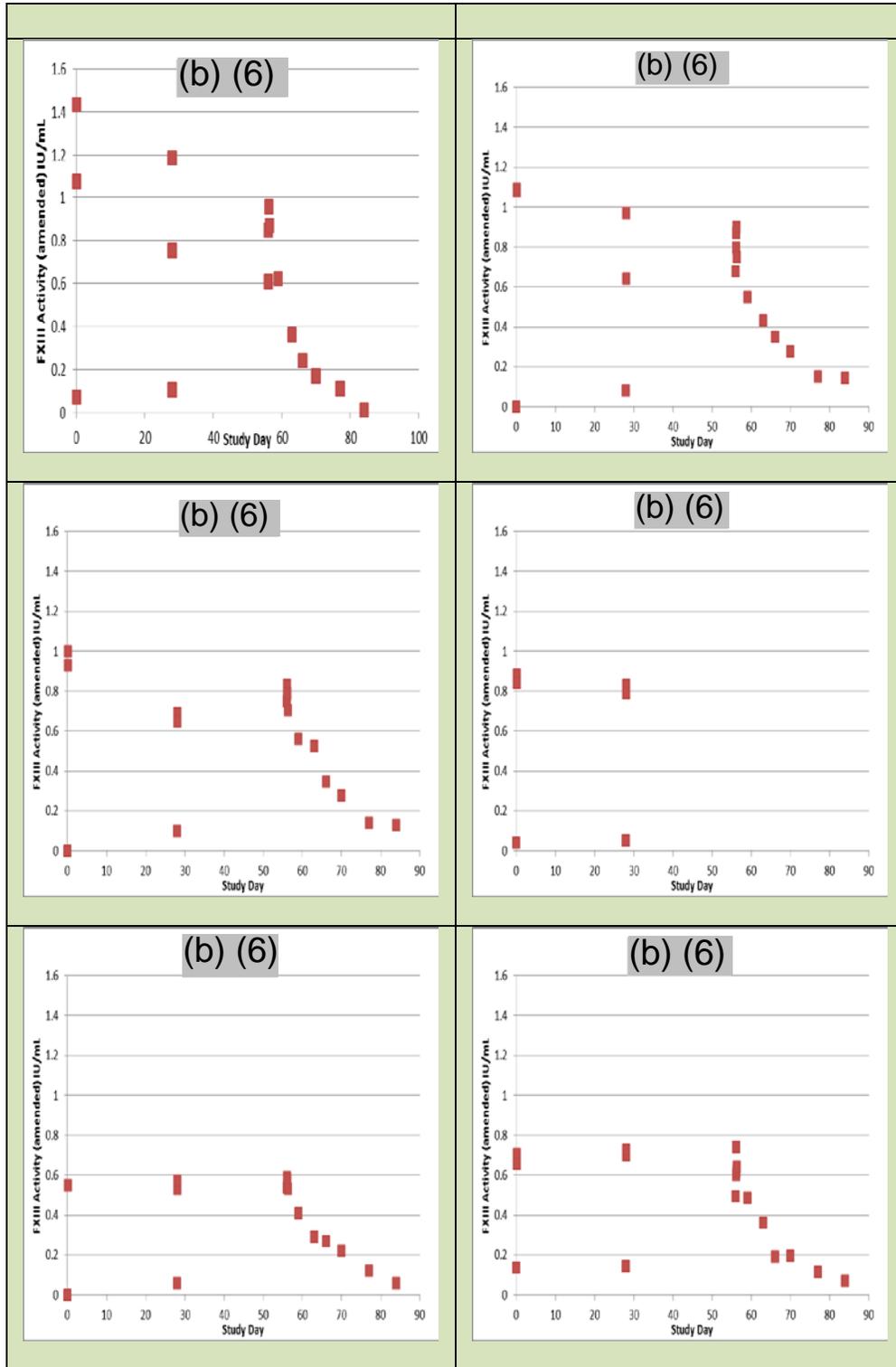
(b) (6)



Appendix 2.1 PK Data for Corifact® from Study BI71023_2002 in STN125385 [CSL Behring]

Dose: 40 IU/kg every 4 weeks X 3

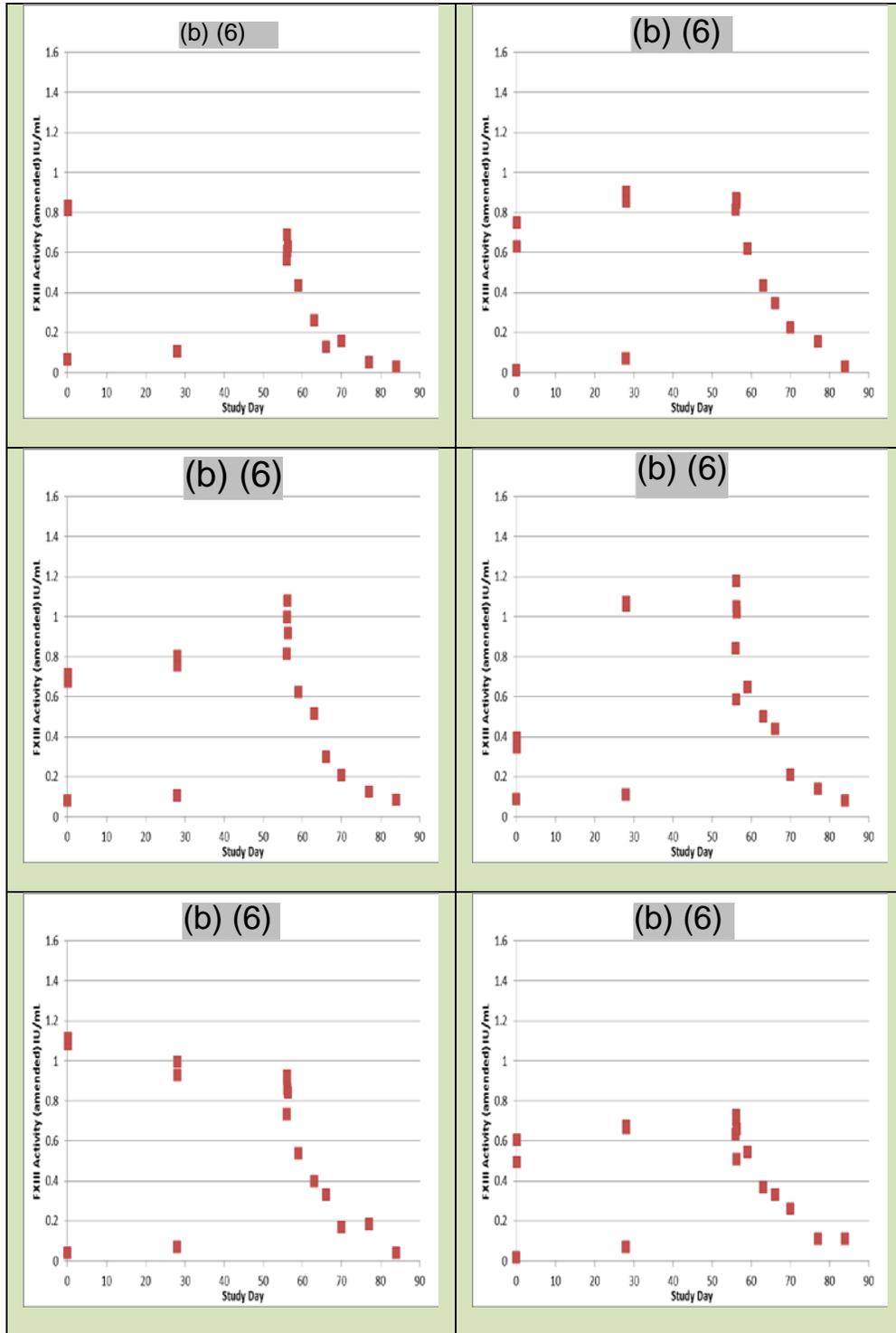
FXIII Activity by Berichrom® Assay [amended]



Appendix 2.1 PK Data for Corifact® from Study BI71023_2002 in STN125385 [CSL Behring]

Dose: 40 IU/kg every 4 weeks X 3

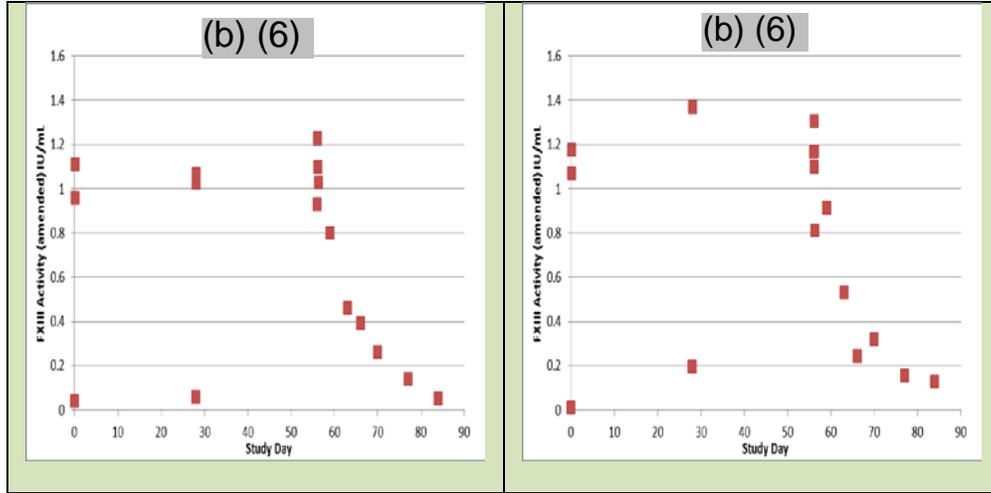
FXIII Activity by Berichrom® Assay [amended]



Appendix 2.1 PK Data for Corifact® from Study BI71023_2002 in STN125385 [CSL Behring]

Dose: 40 IU/kg every 4 weeks X 3

FXIII Activity by Berichrom® Assay [amended]



Treatment Emergent Adverse Events in Study F13CD-1725 by Seriousness and Severity

Appendix 3. Treatment Emergent Adverse Events in Study F13CD-1725 by Seriousness and Severity

		Nonserious								Serious								Grand Total N = 41	
		Mild		Moderate		Severe		Total		Mild		Moderate		Severe		Total			
Body System	Term	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects
Blood and lymphatic system disorders	Anaemia	1	1					1	1									1	1
	Leukopenia	1	1					1	1									1	1
	Lymphadenopathy	1	1					1	1									1	1
	Lymphopenia	1	1					1	1									1	1
	Neutropenia	3	2					3	2									3	2
Blood and lymphatic system disorders Total		7	5					7	5									7	5
Ear and labyrinth disorders	Ear pain	1	1					1	1									1	1
	Vertigo	1	1					1	1									1	1
Ear and labyrinth disorders Total		2	2					2	2									2	2
Eye disorders	Eye inflammation			1	1			1	1									1	1
	Eye pain	1	1					1	1									1	1
	Eye pruritus	1	1					1	1									1	1
	Eye swelling	2	1					2	1									2	1
	Visual impairment	1	1					1	1									1	1
Eye disorders Total		5	4	1	1			6	5									6	5
Gastrointestinal disorders	Abdominal pain	4	2					4	2									4	2
	Aphthous stomatitis	1	1					1	1									1	1
	Dental caries			1	1			1	1									1	1
	Diarrhoea	3	3					3	3									3	3
	Gastritis	1	1					1	1									1	1
	Gastrointestinal disorder			1	1			1	1									1	1
	Haemorrhoids	1	1					1	1									1	1
	Lip ulceration	1	1					1	1									1	1
	Nausea	1	1					1	1									1	1

Treatment Emergent Adverse Events in Study F13CD-1725 by Seriousness and Severity

		Nonserious								Serious								Grand Total N = 41	
		Mild		Moderate		Severe		Total		Mild		Moderate		Severe		Total			
Body System	Term	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects		
	Small intestinal obstruction							0						1	1	1	1		
	Toothache	5	3					5	3										
	Vomiting	3	3					3	3										
Gastrointestinal disorders Total		20	10	2	2			22	11					1	1	1	1		
General disorders and administration site conditions	Chest pain	1	1	1	1			2	2										
	Fatigue	2	2					2	2										
	Injection site pain	2	1					2	1										
	Non-cardiac chest pain							0		1	1					1	1		
	Pain			1	1			1	1										
	Pyrexia	7	7					7	7										
	Xerosis			1	1			1	1										
General disorders and administration site conditions Total		12	8	3	3			15	10	1	1					1	1		
Infections and infestations	Acute sinusitis	1	1					1	1										
	Bronchitis	2	2					2	2										
	Cystitis	2	2					2	2										
	Diverticulitis							0				1	1			1	1		
	Ear infection	1	1					1	1										
	Fungal infection	1	1					1	1										
	Furuncle	1	1					1	1										
	Gastroenteritis viral			1	1			1	1										
	H1N1 influenza			2	2			2	2										
	Hordeolum	1	1					1	1										

Treatment Emergent Adverse Events in Study F13CD-1725 by Seriousness and Severity

		Nonserious								Serious								Grand Total N = 41	
		Mild		Moderate		Severe		Total		Mild		Moderate		Severe		Total		Events	Subjects
Body System	Term	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects		
	Influenza	2	2	3	2			5	4							5	4		
	Molluscum contagiosum	1	1					1	1							1	1		
	Nasopharyngitis	8	7	3	2			11	8							11	8		
	Oral herpes	2	2					2	2							2	2		
	Otitis externa	1	1					1	1							1	1		
	Otitis media			1	1			1	1							1	1		
	Pharyngitis streptococcal	1	1					1	1							1	1		
	Pneumonia	1	1					1	1							1	1		
	Sinusitis			2	2			2	2							2	2		
	Subcutaneous abscess			1	1			1	1							1	1		
	Tracheobronchitis	1	1					1	1							1	1		
	Upper respiratory tract infection	2	2					2	2							2	2		
	Urinary tract infection	3	3					3	3							3	3		
	Vaginal infection	1	1					1	1							1	1		
	Viral infection	1	1	1	1			2	2							2	2		
	Viral rhinitis	1	1					1	1							1	1		
	Vulvovaginal mycotic infection	2	2					2	2							2	2		
Infections and infestations Total		3	1	1	1			50	21			1	1			1	1	51	21
		6	6	4	0														
Injury, poisoning and procedural complications	Animal bite	1	1					1	1							1	1		
	Contusion	2	2					2	2							2	2		
	Drug administration error	1	1					1	1							1	1		
	Excoriation	3	3					3	3							3	3		
	Facial bones fracture			1	1			1	1							1	1		
	Incorrect dose administered	1	4					11	4							11	4		

Treatment Emergent Adverse Events in Study F13CD-1725 by Seriousness and Severity

		Nonserious								Serious								Grand Total N = 41	
		Mild		Moderate		Severe		Total		Mild		Moderate		Severe		Total		Events	Subjects
Body System	Term	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects		
		1																	
	Injury	1	1					1	1									1	1
	Joint injury	1	1					1	1									1	1
	Joint sprain	1	1	1	1			2	2									2	2
	Limb injury	1	1					1	1									1	1
	Road traffic accident								0			1	1			1	1	1	1
	Skin laceration	1	1					1	1									1	1
	Sunburn			1	1			1	1									1	1
	Tooth fracture	2	2					2	2									2	2
	Traumatic haematoma	1	1					1	1									1	1
	Underdose	2	2					2	2									2	2
	Vaccination complication	1	1					1	1									1	1
Injury, poisoning and procedural complications Total		2	1	3	2			32	15			1	1			1	1	33	15
		9	3																
Investigations	Antibody test positive					1	1	1	1	3	3					3	3	4	4
	Blood fibrinogen increased	1	1					1	1									1	1
	Fibrin D dimer increased	1	1					1	1									1	1
Investigations Total		2	2			1	1	3	3	3	3					3	3	6	6
Metabolism and nutrition disorders	Decreased appetite	1	1					1	1									1	1
Metabolism and nutrition disorders Total		1	1					1	1									1	1
Musculoskeletal and connective tissue disorders	Arthralgia	4	4	1	1			5	5									5	5
	Back pain	2	2	2	1	1	1	5	2									5	2
	Bone cyst	1	1	1	1			2	2									2	2
	Bone pain			1	1			1	1									1	1

Treatment Emergent Adverse Events in Study F13CD-1725 by Seriousness and Severity

		Nonserious								Serious								Grand Total N = 41	
		Mild		Moderate		Severe		Total		Mild		Moderate		Severe		Total		Events	Subjects
Body System	Term	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects		
	Bursa disorder	1	1					1	1									1	1
	Costochondritis	1	1					1	1									1	1
	Muscle spasms	1	1					1	1									1	1
	Musculoskeletal pain			1	1			1	1									1	1
	Musculoskeletal stiffness	2	2					2	2									2	2
	Myalgia	2	2					2	2									2	2
	Myosclerosis			1	1			1	1									1	1
	Neck pain	2	2					2	2									2	2
	Pain in extremity	4	4					4	4									4	4
Musculoskeletal and connective tissue disorders Total		20	14	7	4	1	1	28	17									28	17
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Skin papilloma	1	1					1	1									1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Total		1	1					1	1									1	1
Nervous system disorders	Dizziness	1	1					1	1									1	1
	Headache	19	10	1	1			20	11	1	1					1	1	21	12
	Hypoaesthesia	1	1					1	1									1	1
	Sciatica	2	1					2	1									2	1
Nervous system disorders Total		23	10	1	1			24	11	1	1					1	1	25	12
Psychiatric disorders	Depressed mood	1	1					1	1									1	1
Psychiatric disorders Total		1	1					1	1									1	1
Renal and urinary	Dysuria	2	2					2	2									2	2

Treatment Emergent Adverse Events in Study F13CD-1725 by Seriousness and Severity

		Nonserious								Serious								Grand Total N = 41	
		Mild		Moderate		Severe		Total		Mild		Moderate		Severe		Total			
Body System	Term	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects		
disorders	Micturition urgency	1	1					1	1							1	1		
	Pollakiuria	2	2					2	2							2	2		
Renal and urinary disorders Total		5	3					5	3							5	3		
Respiratory, thoracic and mediastinal disorders	Asthma	1	1					1	1							1	1		
	Cough	4	3					4	3							4	3		
	Epistaxis	1	1	1	1			2	1							2	1		
	Nasal congestion	6	5					6	5							6	5		
	Oropharyngeal pain	4	2	2	2			6	4							6	4		
	Rhinorrhoea	1	1					1	1							1	1		
Throat irritation	1	1					1	1							1	1			
Respiratory, thoracic and mediastinal disorders Total		18	11	3	3			21	13							21	13		
Skin and subcutaneous tissue disorders	Blister			1	1			1	1							1	1		
	Ecchymosis	1	1					1	1							1	1		
	Ingrowing nail			1	1			1	1							1	1		
	Itching scar	1	1					1	1							1	1		
	Skin ulcer	1	1					1	1							1	1		
Skin and subcutaneous tissue disorders Total		3	3	2	2			5	5							5	5		
Vascular disorders	Phlebitis superficial	1	1					1	1							1	1		
Vascular disorders Total		1	1					1	1							1	1		
Grand Total		186	29	36	17	2	2	224	32	5	4	2	2	1	1	8	6		

Treatment Emergent Adverse Events in Study F13CD-3720 by Seriousness and Severity

Appendix 4. Treatment Emergent Adverse Events in Study F13CD-3720 by Seriousness and Severity

		Nonserious								Serious						Grand Total N = 33	
		Mild		Moderate		Severe		Total		Moderate		Severe		Total			
Body System	Term	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects
Blood and lymphatic system disorders	Neutropenia	1	1					1	1							1	1
Blood and lymphatic system disorders Total		1	1					1	1							1	1
Cardiac disorders	Cardiovascular disorder	1	1					1	1							1	1
Cardiac disorders Total		1	1					1	1							1	1
Eye disorders	Conjunctivitis	1	1					1	1							1	1
Eye disorders Total		1	1					1	1							1	1
Gastrointestinal disorders	Constipation	1	1					1	1							1	1
	Gastritis	1	1					1	1							1	1
	Gastrooesophageal reflux disease	1	1					1	1							1	1
Gastrointestinal disorders Total		3	2					3	2							3	2
General disorders and administration site conditions	Fatigue					1	1	1	1							1	1
	Inflammation	1	1					1	1							1	1
	Injection site pain	1	1					1	1							1	1
	Pyrexia	1	1	2	1			3	2							3	2
General disorders and administration site conditions Total		3	2	2	1	1	1	6	3							6	3

Treatment Emergent Adverse Events in Study F13CD-3720 by Seriousness and Severity

		Nonserious								Serious						Grand Total N = 33	
		Mild		Moderate		Severe		Total		Moderate		Severe		Total		Events	Subjects
Body System	Term	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects		
Infections and infestations	Bronchitis			1	1			1	1							1	1
	Ear infection	1	1					1	1							1	1
	Gastroenteritis			1	1			1	1							1	1
	Gastroenteritis viral	1	1					1	1							1	1
	Nasopharyngitis	3	3	1	1			4	4							4	4
	Oral herpes	1	1					1	1							1	1
	Otitis media	1	1					1	1							1	1
	Sinusitis	2	2					2	2							2	2
	Tooth infection	1	1					1	1							1	1
	Vulvovaginal mycotic infection			1	1			1	1							1	1
Infections and infestations Total		10	8	4	3			14	9							14	9
Injury, poisoning and procedural complications	Arthropod bite	1	1					1	1							1	1
	Back injury	1	1					1	1							1	1
	Contusion	2	2					2	2							2	2
	Excoriation	2	1	1	1			3	2							3	2
	Fall	3	1					3	1							3	1
	Hand fracture	1	1					1	1							1	1
	Head injury	1	1					1	1							1	1
	Incorrect dose administered	1	1					1	1							1	1

Treatment Emergent Adverse Events in Study F13CD-3720 by Seriousness and Severity

		Nonserious								Serious						Grand Total N = 33	
		Mild		Moderate		Severe		Total		Moderate		Severe		Total		Events	Subjects
Body System	Term	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects		
	Joint sprain	3	2	2	2			5	3							5	3
	Limb injury	3	3					3	3							3	3
	Lip injury	1	1					1	1							1	1
	Medication error	1	1					1	1							1	1
	Overdose	1	1					1	1							1	1
	Skin laceration	1	1					1	1			1	1	1	1	2	1
	Splinter	2	1					2	1							2	1
	Thermal burn	3	3					3	3							3	3
	Traumatic haematoma	2	2					2	2							2	2
	Wound	2	2					2	2							2	2
Injury, poisoning and procedural complications Total		31	13	3	2			34	14			1	1	1	1	35	14
Investigations	Activated partial thromboplastin time prolonged	1	1					1	1							1	1
Investigations Total		1	1					1	1							1	1
Musculoskeletal and connective tissue disorders	Arthralgia	1	1	1	1			2	2							2	2
	Back pain	1	1	1	1			2	2							2	2
	Musculoskeletal discomfort	1	1					1	1							1	1
	Musculoskeletal pain	2	2					2	2							2	2
	Musculoskeletal stiffness	1	1					1	1							1	1

Treatment Emergent Adverse Events in Study F13CD-3720 by Seriousness and Severity

		Nonserious								Serious						Grand Total N = 33	
		Mild		Moderate		Severe		Total		Moderate		Severe		Total		Events	Subjects
Body System	Term	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects		
	Myosclerosis	1	1					1	1							1	1
	Neck pain	2	2					2	2							2	2
	Pain in extremity	2	2					2	2							2	2
	Tendonitis	1	1					1	1							1	1
Musculoskeletal and connective tissue disorders Total		12	10	2	2			14	10							14	10
Nervous system disorders	Carpal tunnel syndrome							0		1	1			1	1	1	1
	Headache	8	5	2	1			10	5							10	5
	Sinus headache	1	1					1	1							1	1
Nervous system disorders Total		9	5	2	1			11	5	1	1			1	1	12	6
Renal and urinary disorders	Haematuria	2	2					2	2							2	2
Renal and urinary disorders Total		2	2					2	2							2	2
Reproductive system and breast disorders	Breast tenderness	1	1					1	1							1	1
Reproductive system and breast disorders Total		1	1					1	1							1	1
Respiratory, thoracic and mediastinal disorders	Cough	1	1					1	1							1	1
	Nasal congestion	1	1					1	1							1	1
	Oropharyngeal pain	2	2					2	2							2	2
Respiratory, thoracic and mediastinal disorders Total		4	3					4	3							4	3
Skin and subcutaneous tissue disorders	Eczema	1	1	1	1			2	2							2	2
	Rash papular	1	1					1	1							1	1

Treatment Emergent Adverse Events in Study F13CD-3720 by Seriousness and Severity

		Nonserious								Serious						Grand Total N = 33	
		Mild		Moderate		Severe		Total		Moderate		Severe		Total		Events	Subjects
Body System	Term	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects		
	Skin irritation	1	1					1	1							1	1
Skin and subcutaneous tissue disorders Total		3	2	1	1			4	3							4	3
Grand Total		82	20	14	6	1	1	97	20	1	1	1	1	2	2	99	20

General Health Screen			
Platelets lower half of normal range	Platelets above normal range	Fibrinogen above normal range	RBCs above or below normal range

Appendix 5. Platelet counts, Fibrinogen levels, and RBC counts by Subject for Study F13CD-1725

Subject Test	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16
(b) (6)	198	157	161	178	150	161	135	194	193	195	180	176	165	222	207	149
	350	339	356	321	352	346	288	353	360	394	365	411	346	372	329	341
	4.45	4.79	4.77	4.43	4.57	4.78	4.73	4.73	4.72	4.82	4.91	4.66	4.86	4.93	4.81	4.73
	302	321	355	352	374	321	251	260	308	355	314	314	321	303	285	354
	269	334	297	316	353	287	271	282	312	341	330	250	326	245	260	269
	5.2	5.36	4.87	5.16	4.92	4.85	4.87	4.5	4.78	4.88	5.09	4.57	4.71	4.91	4.58	4.9
	363	381	325	372	437	324	281	290	325	342	408	349	308	268	389	405
	287	331	321	334	323	300	448	331	294	261	342	333	348	310	331	302
	5.1	5.32	4.89	5.09	5.29	5.23	5.17	5.01	4.84	5.14	5.13	4.92	5.09	4.97	4.94	5.15
	265	207	276	263	293	229	235	240	191	241	237	218	214	233	263	271
	270	280	252	251	280	237	288		274	252	313	248	263	250	308	279
	5.63	5.09	5.11	5.37	5.69	5.7	5.57		5.45	5.28	5.34	5.18	5.74	5.45	5.58	5.31

General Health Screen															
Platelets lower half of normal range	Platelets above normal range	Fibrinogen above normal range	RBCs above or below normal range												

(b) (6)

Subject Test	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16
	251	221	232	230	228	202	229	258	256	226	223	222	221	231	244	228
	353	250	261	263	265	291	265	269	268	305	293	294	314	287	342	289
	5.11	5.03	5.18	5.18	5.23	5.39	5.21	5.16	5.12	5.27	5.1	5.25	5.06	5.15	5	5.07
	417	385	612	453	384	455	383	462	498	455	398	428	446	443	400	415
	447	386	404	445	408	378	365	364	373	398	349	411	354	368	384	418
	4.07	3.88	3.93	3.92		3.96	4.04	4.04	4.03	3.99	3.94	3.87	3.87	4.24	4.09	4.15
	340	299	313	304	318	280	311	297	279	317	268	373	283	317	584	358
	263	235	311	281	258	257	294	271	293	257	303	261	256	285	338	280
	5.13	5	5.17	4.99	5.06	5.05	4.98	5.27	4.91	5.02	5.12	4.61	4.89	4.83	4.67	4.98
	224	233	190	243	221	203	206	240	208	218	211	209	214	190	242	234
	323	314	283	280	303	285	304	278	307	315	310	306	310	300	338	405
	4.42	4.71	4.41	4.61	4.51	4.57	4.39	4.44	4.38	4.54	4.42	4.67	4.63	4.51	4.56	4.47
	217	192	259	212	198	222	196	190	198	208	213	197	212	196	200	209
	408	355	436	343	448	402	383	390	373	386	368	372	366	414	397	350

General Health Screen															
Platelets lower half of normal range	Platelets above normal range	Fibrinogen above normal range	RBCs above or below normal range												

(b) (6)

Subject Test	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16
	4.47	4.09	4.17	4.31	4.12	4.19	4.37	4.43	4.41	4.49	4.39	4.34	4.43	4.26	4.37	4
	267	274	278	306	242	247	247	241	263	239	261	216	210	204	267	228
	333	334	284		310	260	276	257	312	282	359	288	270	257	297	272
	5.37	5.24	4.91	4.79	4.81	5.05	5.35	5.05	4.79	5.19	4.67	4.53	4.53	4.74	4.57	5.05
	249	333	311	327	312	299	266	273	269	311	262	259	274	290	295	267
	347	282	260	268	264	333	305	280	264		249	248	279	400	380	280
	4.53	4.49	4.28	4.54	4.45	4.53	4.25	4.43	4.31	4.7	4.4	4.4	4.6	4.7	4.5	4.5
	369	313	365	351		304	285	280	285	326	347	373	295	275	293	322
	292	278	255	282	268	245	279	295	249	250	271	275	349	294	252	371
	4.82	5		5.31	5.03	5.26	4.95	5.33	5.31	5.53	5.17	5.16	5.38	5.63	5.18	5.18
	335	286	221	344	293	288	353	250	239	247	283	302	274	274	262	321
	274	236	344	253	248	242	278	246	231	250	252	279	251	265	265	318
	4.97	4.88		5.05	5.28	5.3	5.3	4.8	5.1	5.64	5.18	5.61	5.18	5.3	5.34	5.37

General Health Screen															
Platelets lower half of normal range	Platelets above normal range	Fibrinogen above normal range	RBCs above or below normal range												

(b) (6)

Subject Test	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16
						4		7	3							
	181	185	236	204		222	206	202	201	185	191	163	160	255	187	187
	402	348	371	373	382	404	338	342	351	345	276	324	268	254	349	391
	4.93	4.92	4.93	4.81	5.2	5.4 6	5.1	4.9 6	4.9 5	4.59	5.09	5.02	5.21	4.55	5.2	4.95
	245	217	279	272		291	256	220	278	247	245	191	229	209	220	258
		268	282	288	244	320	331	326	240	282	248	220	298	233	235	373
	4.35	4.5	4.49	4.39	4.53	4.4 4	4.38	4.2 6	4.3 6	4.32	4.54	4.28	4.44	4.5	4.57	4.15
	279	350	290	346	305	312	316	264	334	303	290	237	231		323	299
		316	279	264	224	285	257	228	250	246	227	237	283	253	258	255
	4.59	4.6	4.52	4.5	4.59	4.6 7	4.61	4.6 7	4.4 5	4.45	4.54	4.58	4.6	4.45	4.54	4.55
	238	279	256	233	221	232	244	213	248	222	202	215	186	237	224	288
	443	585	421	504	431	643	404	460	451	474	416	425	405	445	453	461
	4.41	4.6	4.31	4.6	4.43	4.8 4	4.65	4.5 8	4.3 4	4.44	4.39	4.72	4.41	4.47	4.52	4.51
	209	200	203	199	190	238	199	176	188	162	211		171	211		193

General Health Screen															
Platelets lower half of normal range	Platelets above normal range	Fibrinogen above normal range	RBCs above or below normal range												

(b) (6)

Subject Test	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16
	374	312	346	285	312	391	331	336	335	300	391	303	314	345		339
	5.26	5.17	5.41	5.1	5.04	5.05	5.07	5.02	4.75	5.14	5.07	5.07	5.11	5.02		4.75
	216	219	226	223	216	221	213	219	209	186	176	192	175	233	243	227
	308	246		335	288	339	304	303	294	273	259	278	267	350	263	339
	6.05	5.89	6.11	5.97	5.91	6.18	5.88	5.96	5.73	5.76	5.89	5.87	5.63	5.88	5.61	6.06
	176	208	169	165	202	227	214		191	190	211	186	234	229	184	176
	239	256		235	216	247	245	213	267	236	250	255	274	272	239	246
	5.11	5.09	5.27	5.48	5.17	5.69	5.27	5.39	4.98	5.59	5.46	5.43	5.5	5.52	5.25	5.14
	310	228	300	280	250	245										269
	378	263	273	328	313	349										299
	5.19	5.13	5.26	5.84	5.06	5.03										4.84
	270	253	243	264	233	233	236	243	228	240	238	268	227	260	252	296
	357	332	312	285	302	271	327	350	311	311	362	333	557	348	334	404

General Health Screen															
Platelets lower half of normal range	Platelets above normal range	Fibrinogen above normal range	RBCs above or below normal range												

(b) (6)

Subject Test	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16
	5.26	5.34	5.03	5.17	5.26	4.91	5.31	5.09	5.13	5.02	5.13	4.88	5.05	5.14	5.02	5.32
	234	224	216	248	225	217		256	196	206	215	220	242	229	208	221
	240	244	246	238	227	218	213	240	219	235	251	238	244	226	243	231
	5.5	5.2	5.2	5.6	5.3	5.4	5.3	5.2	5.1	5.4	5.4	5.4	5.6	5.5	5.5	5.4
	399	424	390	379	420	360		386	448	376	435	383	390		402	440
	240	244	236	246	228	239	235	249	298	242	267	251	228	253	236	241
	4.6	4.7	4.7	4.7	4.5	4.8	4.6	4.8	4.7	4.6	4.9	4.5	4.5	4.6	4.3	4.6
	270	279	284	267	283	285		289	308	287	273	310	280	277	282	239
	289	270	243	265	260	271	256	284	318	250	236	306	284	277	273	301
	4.77	4.55	4.68	4.62	5	4.91	4.7	4.67	4.86	4.87	4.72	4.88	4.88	4.54	4.73	4.63
	369	362	327	363	379			350	329							
	245	245	238	270	271	251		287	274							
	4.5	4.3		4.36	4.53	4.23		4.51	4.41							

General Health Screen															
Platelets lower half of normal range	Platelets above normal range	Fibrinogen above normal range	RBCs above or below normal range												

(b) (6)

Subject Test	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16
	354	295	373	383	307	240	340		292	282	302	306	317	284		317
	246	288	557	335	416	247	304	287	328	262	316	312	393	253	271	280
	5.56	5.57	5.23	5.58	5.6	5.28	5.54	5.42	5.19	5.37	5.18	5.73	5.31	5.35	5.23	5.27
	274	255	321	288	235	297	277	255	256	282	277					336
	321	314		256	260	257	267	267	272	282	291					301
	4.08	4.2	4.23	4.17	4.19	4.31	4.15	3.9	3.93	4.07	3.85					3.88
	367		317	309	349	370	338	348	371	354	348	386	372	367	289	333
	281	251	247	253	253	237	264	280	318	277	272	310	228	271	246	352
	5.24	5.63	5.27	5.11	5.22	5.23	5.4	5.3	5.16	5.5	5.42	5.62	5.48	5.5	5.06	5.26
	255		250	247	255	212	286	257	256	271	274	270	236	289	244	267
	362	278	242	248	238	240	281	240	245	253	258	258	236	250	258	294
	5.02	5.04	4.67	4.8	5.09	4.99	5.41	4.87	4.79	4.73	4.84	5.12	4.95	5.03	5.1	5.03
	284				259	268	228	262	280	267	281	270			264	272
		378	341	360	342	411	352	374	400	330	363	428	431	345	370	350

General Health Screen			
Platelets lower half of normal range	Platelets above normal range	Fibrinogen above normal range	RBCs above or below normal range

(b) (6)

Subject Test	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16
	4.4	4.7	4.4	4.5	4.4	4.4	4.5	4.5	4.4	4.3	4.4	4.5	4.6	4.5	4.5	4.6
	183	265	217	228	201	186	199	218	223	201	228	199	225	213	193	186
	256	292	260	250	233	229	260	217	210		238	239	246		238	263
	5.22		5.01	4.97	4.5	4.4 3	4.65	4.8 8	4.6 4	4.48		4.49	4.79	4.62	4.63	4.61
	214	199	216	240	198	232	231	217	216	215	216	260	260	226	226	
	328	245	280	266	243	262	250	268	225	288	246	284	326	276	330	249
	4.13	3.9	4.01	4.1	3.79	3.8 9	3.63	3.7 6	3.8 1	4.07	3.97	4.02	4.27	4.03	4.41	4.21
	197	177	269	183	195	208	190	146	169	143	178	154	189	199	188	
	299	242	472	371	259	279	263	237	259	303	256	367	271	258	250	296
	4.52	4.57	4.58	4.59	4.29	4.5	4.44	4.7	4.7 8	4.46	4.51	5.09	5.17	5.03	4.86	5.06
	269	281	269	223												284
	330	215	211	223												235
	4.77	5.02	4.67	4.68												4.81

General Health Screen															
Platelets lower half of normal range	Platelets above normal range	Fibrinogen above normal range	RBCs above or below normal range												

(b) (6)

Subject Test	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16
	280		324	309	330	319	356	325	331	366	302	335	366	362	357	399
	515	270	350	285	262	329	311	304	256	299	396	331	309	344	307	277
	4.18	4.42	4.52	4.15	4.22	4.35	4.38	4.33	4.25	4.38	4.28	4.21	4.6	4.56	4.64	4.36
	303	378	386	381	382	359	415	376	380	392	442	423	383	396	299	369
	258	255	247	293	263	249	259	250	283		294	272	301		247	
	4.6	4.85	4.82	4.79	4.87	5.07	5.16	4.94	4.94	5	4.77	4.88	5.02	5.13	5.24	5
	300	296		334	299	317	295	301	311	306	322	260			277	268
	333	341	314	342	323	346	351	280	268	316	287	319	249	154	295	255
	5.25	5.25	5.08	5.04	5.19	5.32	4.95	5.11	4.99	5.08	5.22	5.23	5.08	5.14	4.9	5.26
	251	288	253	232	220	275	262	250	261	242	251	263	255	252	255	274
	221	255	239	221	255	233	238	239	237	225	250	224	245	230	243	233
	4.31	4.67	4.11	4.18	4.2	4.21	4.17	4.61	4.31	4.46	4.12	4.21	4.18	4.18	4.22	4.46
	202	178	190	154	169	152	194	183	177	148	216	149	149	183	187	192

General Health Screen			
Platelets lower half of normal range	Platelets above normal range	Fibrinogen above normal range	RBCs above or below normal range

Subject Test	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16
(b) (6)																
	245	265	274	241	241	258	243	238	257	221	257	248	250	239	238	272
	5.46	5.49	5.48	5.27	5.46	5.24	5.25	5.23	5.22	5.08	5.18	5.27	5.39	5.4	5.51	5.16
	241	193		229	244	257	213	237	251	242	236	225	257	271	229	246
	319	332	333	300	126	242	299			284	321	291	266	318	251	276
	5.15	5.06	5.11	5.15	5.25	5.11	5.05	4.92	5.26	5.21	5.08	5.34	5.19	5.15	5.24	5.24

Integrated anti-FXIII Antibody Results for Studies F13CD-1725 and F13CD-3720								
	Reactive in Tier 1 Test		Repeat Reactive in Tier 1 Test		Repeat Reactive in Tier 1 Test Antigen Non-Specific in Tier 2 Test		Repeat Reactive in Tier 1 Test Antigen Specific in Tier 2 Test	'Blue' Indicates Titer Measured in Tier 3 Test

Subject	← 52 Weeks → F13CD-1725														F13CD-3720 → → → → → → → → → → → → → → → →													
	(b) (6)	[Red bar]														[Red bar]												
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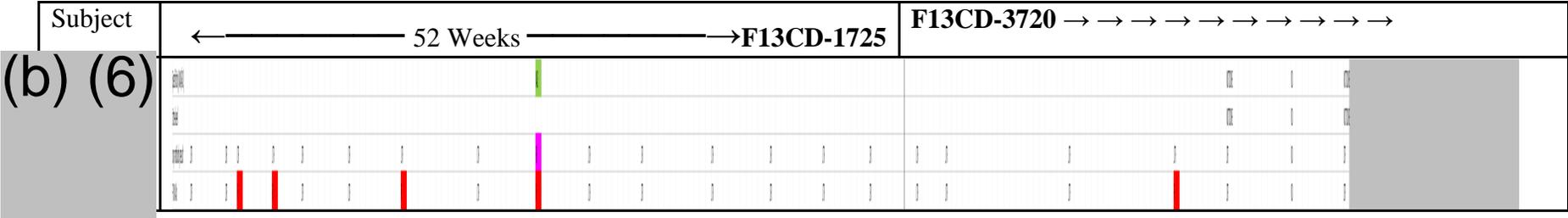
Integrated anti-FXIII Antibody Results for Studies F13CD-1725 and F13CD-3720							
	Reactive in Tier 1 Test		Repeat Reactive in Tier 1 Test		Repeat Reactive in Tier 1 Test Antigen Non-Specific in Tier 2 Test	Repeat Reactive in Tier 1 Test Antigen Specific in Tier 2 Test	'Blue' Indicates Titer Measured in Tier 3 Test

Subject	← 52 Weeks → F13CD-1725												F13CD-3720 → → → → → → → → → → → →											
	(b) (6)	[Detailed grid of antibody test results for multiple subjects across two studies. The grid shows various colored bars (red, green, blue, orange) indicating reactivity in different tiers and tests. Some cells are shaded grey, indicating missing or unreported data. The results are organized by subject and time point within each study.]																						

Integrated anti-FXIII Antibody Results for Studies F13CD-1725 and F13CD-3720								
	Reactive in Tier 1 Test		Repeat Reactive in Tier 1 Test		Repeat Reactive in Tier 1 Test Antigen Non-Specific in Tier 2 Test		Repeat Reactive in Tier 1 Test Antigen Specific in Tier 2 Test	'Blue' Indicates Titer Measured in Tier 3 Test



Integrated anti-FXIII Antibody Results for Studies F13CD-1725 and F13CD-3720								
	Reactive in Tier 1 Test		Repeat Reactive in Tier 1 Test		Repeat Reactive in Tier 1 Test Antigen Non-Specific in Tier 2 Test		Repeat Reactive in Tier 1 Test Antigen Specific in Tier 2 Test	'Blue' Indicates Titer Measured in Tier 3 Test



Appendix 7. Pre-Dose to 1-Hour Post-Dose Change in B Subunit Concentration (µg/mL) by 1-Hour Change in FXIII Berichrom Activity by Subject and Study Visit

Subject	Visit	1-Hour FXIII Activity					Red background indicates the decrease in B Subunit level was small (bottom 10%) N.B.: Switching to plasma-derived FXIII will result in a post-dose increase in B subunit level, contrary to the rFXIII effect																		
		-0.6	-0.4	-0.3	-0.2	-0.1	0.1	0.2	0.3	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1	1.1	1.2	1.3	2.8	3.1	5.3		
(b) (6)	VISIT 2												-4.66												
	VISIT 4													-4.47											
	VISIT 5												-3.14												
	VISIT 6													-3.26											
	VISIT 7													-2.34											
	VISIT 8													-2.33											
	VISIT 9												-2.58												
	VISIT 10													-3.75											
	VISIT 11														-3.8										
	VISIT 12												-4.88												
	VISIT 13												-4.1												
	VISIT 14													-4.64											
	VISIT 15												-2.41												
	(b) (6)	VISIT 2												-3.53											
		VISIT 4														-2.78									
VISIT 5														-2.33											
VISIT 6															-6.67										
VISIT 7														-2.34											
VISIT 8															-3.55										
VISIT 9													-2.37												
VISIT 10												-2.69													
VISIT 11															-2.45										
VISIT 12													-3.48												
VISIT 13													-3.1												
VISIT 14														-4.73											
VISIT 15																-3.01									
VISIT 2																-5.02									

Subject	Visit	1-Hour FXIII Activity					Red background indicates the decrease in B Subunit level was small (bottom 10%) N.B.: Switching to plasma-derived FXIII will result in a post-dose increase in B subunit level, contrary to the rFXIII effect																	
		-0.6	-0.4	-0.3	-0.2	-0.1	0.1	0.2	0.3	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1	1.1	1.2	1.3	2.8	3.1	5.3	
(b) (6)	VISIT 4													-3.95										
	VISIT 5														-2.85									
	VISIT 6														-4.36									
	VISIT 7													-2.7										
	VISIT 8															-3.99								
	VISIT 9													-2.7										
	VISIT 10													-3.44										
	VISIT 11														-3.51									
	VISIT 12															-4.25								
	VISIT 13														-5.53									
	VISIT 14														-6.64									
	VISIT 15																-4.47							
	VISIT 2																-3.79							
	VISIT 4														-2.17									
	VISIT 5														-5.01									
VISIT 6					-4.48																			
VISIT 7												1.5												
VISIT 8										0.73														
VISIT 9				-5.11																				
VISIT 10				-5.4																				
VISIT 11				-6.02																				
VISIT 12										-0.43														
VISIT 13				-7.74																				
VISIT 14				-5.67																				
VISIT 15				-5.79																				
VISIT 2													-2.73											
VISIT 4												-2.92												
VISIT 5													-2.95											
VISIT 6														-2.49										

Subject	Visit	1-Hour FXIII Activity					Red background indicates the decrease in B Subunit level was small (bottom 10%) N.B.: Switching to plasma-derived FXIII will result in a post-dose increase in B subunit level, contrary to the rFXIII effect																	
		-0.6	-0.4	-0.3	-0.2	-0.1	0.1	0.2	0.3	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1	1.1	1.2	1.3	2.8	3.1	5.3	
(b) (6)	VISIT 7															-2.89								
	VISIT 8														-3.6									
	VISIT 9														-2.18									
	VISIT 10														-2.22									
	VISIT 11														-3.61									
	VISIT 12														-3.29									
	VISIT 13														-3.02									
	VISIT 14														-2.14									
	VISIT 15													-2.96										
	VISIT 2																-3.51							
	VISIT 4															-8.3								
	VISIT 5																-3.43							
	VISIT 6																-2.8							
	VISIT 7																-2.96							
	VISIT 8																-3.4							
	VISIT 9																		-2.71					
	VISIT 10											-2.22												
	VISIT 11																		-9.48					
	VISIT 12															-3.19								
	VISIT 13												-2.74											
	VISIT 14																-3.22							
	VISIT 15																-2.89							
	VISIT 2																-3.13							
	VISIT 4																	-3.81						
	VISIT 5																-3.57							
VISIT 6														-3.48										
VISIT 7																	-2.57							
VISIT 8																	-4.43							
VISIT 9																	-6.1							

Subject	Visit	1-Hour FXIII Activity					Red background indicates the decrease in B Subunit level was small (bottom 10%) N.B.: Switching to plasma-derived FXIII will result in a post-dose increase in B subunit level, contrary to the rFXIII effect																			
		-0.6	-0.4	-0.3	-0.2	-0.1	0.1	0.2	0.3	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1	1.1	1.2	1.3	2.8	3.1	5.3			
(b) (6)	VISIT 4															-4.49										
	VISIT 5														-5.07											
	VISIT 6													-6.11												
	VISIT 7															-4.17										
	VISIT 8															-3.24										
	VISIT 9															-7.49										
	VISIT 10															-2.91										
	VISIT 11																									
	VISIT 12																									
	VISIT 13																									
	VISIT 14																									
	VISIT 15																									
	VISIT 2																									
	VISIT 4																									
	VISIT 5																									
	VISIT 6																									
	VISIT 7																									
	VISIT 8																									
	VISIT 9																									
	VISIT 10																									
	VISIT 11																									
	VISIT 12																									
	VISIT 13																									
	VISIT 14																									
	VISIT 15																									
VISIT 2																										
VISIT 4																										
VISIT 5																										
VISIT 6																										
VISIT 2																										
VISIT 4																										
VISIT 5																										
VISIT 6																										

Subject	Visit	1-Hour FXIII Activity				Red background indicates the decrease in B Subunit level was small (bottom 10%) N.B.: Switching to plasma-derived FXIII will result in a post-dose increase in B subunit level, contrary to the rFXIII effect																		
		-0.6	-0.4	-0.3	-0.2	-0.1	0.1	0.2	0.3	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1	1.1	1.2	1.3	2.8	3.1	5.3	
(b) (6)	VISIT 13												-2.96											
	VISIT 14													-2.99										
	VISIT 2														-2.84									
	VISIT 4													-4.81										
	VISIT 5															-4.08								
	VISIT 6									-3.84														
	VISIT 7												-3.79											
	VISIT 8															-3.54								
	VISIT 9																-3.74							
	VISIT 10				-1.73																			
	VISIT 11															-4.14								
	VISIT 12												-3.45											
	VISIT 13														-3.41									
	VISIT 14													-4.8										
	VISIT 15													-6.22										
	VISIT 2														-2.67									
	VISIT 4								-3.14															
	VISIT 5									-2.09														
	VISIT 6										-5.54													
	VISIT 7													-3.94										
	VISIT 8												-4.32											
	VISIT 9												-3.95											
	VISIT 10											-3.36												
	VISIT 11															-4.65								
	VISIT 12							-4.2																
VISIT 13													-3.89											
VISIT 14															-4.14									
VISIT 15													-5.38											
VISIT 2											-2.03													

Subject	Visit	1-Hour FXIII Activity					Red background indicates the decrease in B Subunit level was small (bottom 10%) N.B.: Switching to plasma-derived FXIII will result in a post-dose increase in B subunit level, contrary to the rFXIII effect																		
		-0.6	-0.4	-0.3	-0.2	-0.1	0.1	0.2	0.3	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1	1.1	1.2	1.3	2.8	3.1	5.3		
(b) (6)	VISIT 4																								
	VISIT 5																								
	VISIT 6																								
	VISIT 7																								
	VISIT 8																								
	VISIT 9																								
	VISIT 10																								
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VISIT 13																									
VISIT 14																									
VISIT 15																									
VISIT 2																									
VISIT 4																									
VISIT 5																									
VISIT 6																									

Subject	Visit	1-Hour FXIII Activity				Red background indicates the decrease in B Subunit level was small (bottom 10%) N.B.: Switching to plasma-derived FXIII will result in a post-dose increase in B subunit level, contrary to the rFXIII effect																		
		-0.6	-0.4	-0.3	-0.2	-0.1	0.1	0.2	0.3	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1	1.1	1.2	1.3	2.8	3.1	5.3	
(b) (6)	VISIT 8												-6.05											
	VISIT 9													-3.91										
	VISIT 2												-2.41											
	VISIT 4													-4.07										
	VISIT 5															-2.46								
	VISIT 6										-2.68													
	VISIT 7												-3.47											
	VISIT 8													-3.5										
	VISIT 9											-3.48												
	VISIT 10												-5.39											
	VISIT 11												-3.62											
	VISIT 12											-2.13												
	VISIT 13														-2.93									
	VISIT 14												-3.69											
	VISIT 15										-3.15													
	VISIT 2												-2.06											
	VISIT 4										-2.23													
	VISIT 5												-2.6											
	VISIT 6										-1.22													
	VISIT 7													-2.79										
	VISIT 8											-3.89												
	VISIT 9					-5.2																		
	VISIT 10		-4.34																					
	VISIT 11												-3.14											
	VISIT 2												-4.87											
	VISIT 4												-4.93											
	VISIT 5												-8.55											
	VISIT 6											-3.14												
	VISIT 7												-3.6											

Subject	Visit	1-Hour FXIII Activity				Red background indicates the decrease in B Subunit level was small (bottom 10%) N.B.: Switching to plasma-derived FXIII will result in a post-dose increase in B subunit level, contrary to the rFXIII effect																		
		-0.6	-0.4	-0.3	-0.2	-0.1	0.1	0.2	0.3	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1	1.1	1.2	1.3	2.8	3.1	5.3	
(b) (6)	VISIT 15														-3.35									
	VISIT 2														-4.15									
	VISIT 4															-4.08								
	VISIT 5													-7.67										
	VISIT 6											-6.16												
	VISIT 7								-2.01															
	VISIT 8														-4.09									
	VISIT 9													-5										
	VISIT 10																							-4.6
	VISIT 11													-5.29										
	VISIT 12														-6.71									
	VISIT 13														-8.11									
	VISIT 14																							-8.4
	VISIT 15		-5.08																					
	VISIT 2											-3.25												
	VISIT 4															-4.17								
	VISIT 5			-4.23																				
	VISIT 6															-4.44								
	VISIT 7															-5.13								
	VISIT 8															-4.3								
VISIT 9															-3.55									
VISIT 10												-2.02												
VISIT 11															-4.75									
VISIT 12															-3.91									
VISIT 13			-3.41																					
VISIT 15														-4.66										
VISIT 2										-2.77														
VISIT 4											-2.17													
VISIT 5											-8.46													

Subject	Visit	1-Hour FXIII Activity					Red background indicates the decrease in B Subunit level was small (bottom 10%) N.B.: Switching to plasma-derived FXIII will result in a post-dose increase in B subunit level, contrary to the rFXIII effect																	
		-0.6	-0.4	-0.3	-0.2	-0.1	0.1	0.2	0.3	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1	1.1	1.2	1.3	2.8	3.1	5.3	
(b) (6)	VISIT 9														-4.91									
	VISIT 10											-4.57												
	VISIT 11													-4.65										
	VISIT 12													-4.37										
	VISIT 13														-5.26									
	VISIT 14																-6.44							
	VISIT 15												-4.75											