Application Type	Original Application
STN	125426/0
CBER Received Date	April 6, 2012
PDUFA Goal Date	February 4, 2013
Division / Office	DH /OBRR
Priority Review	No
Reviewer Name(s)	Irwin Feuerstein
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Emergent BioSolutions / Cangene
Established Name	Coagulation Factor IX (Recombinant), IB1001
(Proposed) Trade Name	IXINITY
Pharmacologic Class	Coagulation factor
Formulation(s), including Adjuvants, etc	Intravenous injection
Dosage Form(s) and Route(s) of Administration	Lyophilized powder for injection
Dosing Regimen	500, 1000, 1500 IU/vial
Indication(s) and Intended Population(s)	Control and prevention of bleeding episodes and perioperative management in patients with hemophilia B
Orphan Designated (Yes/No)	No

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1. EXECUTIVE SUMMARY

The product (IB1001/IXINITY) is a recombinant human factor IX manufactured in Chinese hamster ovary (CHO) cells. IB1001 is a lyophilized recombinant factor IX intended for intravenous administration as a replacement therapy for control and prevention of bleeding episodes and perioperative management of hemophilia B patients undergoing surgery.

Data from a single combined phase 1/2/3 study that included subjects on prophylactic and on-demand treatment as well as subjects undergoing surgery were submitted in support of licensure for the proposed indications. The clinical development program for IB1001 included a randomized cross-over comparative PK study with BeneFIX; a non-randomized open-label treatment phase where subjects received either prophylaxis or on-demand for at least 50 exposure days (ED),and a perioperative prophylaxis study. Data from pediatric subjects were also included.

A total of 77 subjects were enrolled in one or more study phases and 68 of these subjects were used for analysis of safety and efficacy in the treatment phase. Total exposure was 9,641 infusions (median 116 infusions per subject) and 112 days. For Treatment and Continuation Phases, exposure was 9,395 days (median 128 days per subject). Overall, 449 adverse events were reported in 58 subjects (75% of subjects) in the entire IB001-01 study. There were 14 serious events, all considered unrelated. No deaths were reported. The most commonly reported events in > 10% of subjects were headaches (17%), arthralgia (16%), pyrexia (13%), nasopharyngitis (12%), and limb injury (10%). Events were mild in 68%, moderate in 27%, or severe in 5%. Adverse reactions were determined in 15 of 449 AEs (3% of events were reactions) in 7 of 77 subjects (9% of subjects had reactions). The only adverse reaction reported in more than one subject was headache. Reactions were mild (n = 8, in six subjects) or moderate (n = 7, in two subjects). The frequency of adverse events per injection was < 1%. Thrombotic events, hypersensitivity, anaphylaxis, and nephrotic syndrome were not reported. No subject developed inhibitory antibody to factor IX. Non-inhibitory antibodies developed in 27% of subjects (21/ 77) with no clinical consequences.

Efficacy was demonstrated across all indications. The PK Phase and Repeat PK Study demonstrated noninferiority to marketed product and no deterioration in recovery. Performance for the treatment of bleeding episodes was acceptable as reported by investigators and subjects. The Surgery Substudy demonstrated target levels for factor IX, acceptable performance as assessed by investigators, and outcomes as expected or better than expected in every procedure. Because of orphan exclusivity by another product, a prophylaxis indication cannot be claimed.

Recommendation:
The overall committee recommendation is that a complete reponse letter be issued because of product and inspectional issues. From the clinical reviewer perspective, the application for IXINITY has shown acceptable safety and efficacy of the current product for the indications claimed and could be approvable pending satisfactory resolution of the issues raised in the letter ready comments listed below along with subsequent labeling review.

Letter-Ready Comments:

1. Mean annualized bleeding rates are reported as square-root transformed numbers, rather than on original scale, in the prescribing information and other locations in the submission. FDA information request of 2014-05-22 recommended updating the study report to use original scale to report the mean annualized bleeding rates. You declined to update to original scale in Sequence e0029 dated 2014-05-29, stating that use of transformed numbers was previously agreed upon. FDA did agree with the Statistical Analysis Plan that square-root transformed numbers could be used for statistical calculations as data transformation is an acceptable approach to compare two treatment regimens/groups for non-normalized data. However, FDA does not allow use of square-root transformed numbers as the primary or only presentation of mean efficacy rates, particularly in labeling, as they are not clinically relevant and may cause confusion. Furthermore, you have presented only the square-root transformed mean annualized bleeding rates in the prescribing information. You have pointed out that the same data transformation was used in the statistical analysis in the ADVATE licensing application, but note that only results based on data on the original scale are reported in the ADVATE prescribing information.

   Again, please update your submission to use original scale for presentation of mean annualized bleeding rates and any other efficacy measures. This update should be applied to all documents including prescribing information, synopses, summaries, and full study report. In instances where only one mean efficacy rate data point is provided, it should be original scale. In instances where both original and transformed mean efficacy rates are presented, original scale should be the primary presentation and transformed rates should be clearly indicated.

2. Section 11.4.1.2.1.1 in Amendment 125426/0.23 Sequence e0024 states that some data from bleeding diaries could not be obtained in time for the report. Please submit the data from these diaries.

3. In the latest version of the prescribing information from Sequence 0027, on Page 16 in the section on *Treatment of Bleeding Episodes*, it says “Majority of the bleeds, 360 (70.9%) resolved after a single infusion of IXINITY and 65 (13.0%) after two infusions.” However, the *Summary of Clinical Efficacy* states (1) for prophylaxis, “Majority of bleeds 189 (37.2%) resolved after a single infusion and 41 (8.1%) after two infusions,” and (2) on-demand “Majority of bleeds 169 (33.3%) resolved after a single infusion and 25 (4.9%) after two infusions.” Please check the numbers and percentages of infusions in all documents and ensure that these are accurately captured in the package insert.

4. Page 52 of the *Summary of Clinical Safety* states that nine events were probably related and seven events were possibly related to study drug, which should add up to 16 adverse reactions. However, only 15 reactions are reported. Please clarify.

5. In your related adverse drug reactions (ADR), you include one case of noninhibitory anti-FIX antibody. Please provide a narrative of this case (or provide its location in the submission) and explain why this case was selected as an ADR while the other subjects who developed noninhibitory anti-FIX antibodies

were not categorized as ADRs.

6. The number of subjects who developed non-neutralizing anti-FIX antibodies during the study, and were negative at baseline, is not clear. Page 50 in the *Summary of Clinical Safety says that* 21 subjects (27%) had non-inhibitory antibodies not present at baseline, but page 91 in the same document says that 5 out of those 21 subjects were positive at baseline. Please clarify.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

- Hemophilia B (Christmas disease) is a rare hereditary blood disorder caused by deficiency or dysfunction of factor IX resulting in bleeding secondary to abnormal clot formation. Hemophilia B occurs in approximately 1 in 50,000 people. Hemophilia B constitutes 20% of the total hemophilia A and B population. It is typically an X-linked recessive inherited trait carried by women heterozygous for the gene. Spontaneous mutations occur in one-third to one-half of cases, more commonly in severe cases. Children present after circumcision, intramuscular immunization, trauma, or with intracranial hemorrhage.

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

- Treatments for hemophilia B require replacement with a form of factor IX. Factor IX treatments include human plasma products such as fresh-frozen plasma or prothrombin complex concentrates. Monoclonally purified, recombinant factor IX preparations are now available and are the mainstay of therapy. Bypassing agents are available in the instance of inhibitor formation but these are not first-line therapy.

2.3 Safety and Efficacy of Pharmacologically Related Products

- At the time of submission, the only FDA-approved recombinant factor IX product was BeneFIX, which was approved in 1997. There are two plasma derived Factor IX products approved: Alphanine and Mononine.
- During the review process, Rixubis recombinant factor IX was approved. Rixubis is manufactured by Baxter International. Rixubis was approved for prophylaxis in hemophilia B and was granted orphan exclusivity for the prophylaxis indication.

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

- Human subjects were exposed for the first time to this product under the current IND.

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

- See Appendix A for timeline. The evidence for safety and efficacy for this product was collected under IND 13551.

2.6 Other Relevant Background Information

- The study was placed on clinical hold in the U.S. 2012-07.
- In the U.K., high-titer subjects stopped treatment, but others could continue with monitoring.
- In India, all subjects initially stopped treatment and were provided marketed factor IX product. After review, some subjects were allowed to stay on orig-IB1001 at the discretion of investigators and subjects. [Source: 125426/0.23/e0024, *Supplemental Clinical Study Report*, p. 28]
- The two active subjects in Italy and one in Poland elected to terminate participation.
- No subjects were active in Israel and France around the time of clinical hold.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

- Submission quality and completeness were acceptable from the clinical perspective. IB1001 is produced in Chinese Hamster Ovary (CHO) cells and has a primary amino acid sequence identical to the Thr148 allelic form of plasma-derived factor IX. It is a 415 amino acid glycoprotein with a molecular weight of 55,000 daltons. Please refer to CMC reviewer's memo.

3.2 Compliance With Good Clinical Practices And Submission Integrity

- Informed consents and investigator brochures were modified in Amendment 11 of the protocol. No objections to these documents were raised.

3.3 Financial Disclosures

- The original applicant/sponsor was Inspiration Biopharmaceuticals Inc. The application had been taken over by Cangene Corporation, which was subsequently acquired by, and currently doing business as, Emergent BioSolutions.

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

4.1 Chemistry, Manufacturing, and Controls

- DMPQ memo is here. There are three comments regarding manufacturing, with responses needed by 2014-05-20.
- Section 3.2.P.2.5, val_ev_0178_rep_v1, p. 6/20, discusses the drug substance and product factor IX validations. (b) (4)

- BeneFIX is also made in CHO cells.

4.2 Assay Validation

- Please refer to the memo from the product reviewer.

4.3 Nonclinical Pharmacology/Toxicology

- Please refer to the memo from the product reviewer regarding comparability and bridging studies between original and modified product.

4.4 Clinical Pharmacology

- Please refer to the memo from the clinical pharmacologist.

4.5 Statistical

- Please refer to the memo from the statistical reviewer, who has information requests to the applicant. The statistical information request of 2014-05-22 inquired about two issues. The first issue was use of square-root transformed numbers in the label rather than normal scale. FDA had previously agreed to the use of transformed data in the statistical calculations, but the company has extended this to mean that they could use transformed numbers as means and medians in efficacy in labeling. The IR instructed the company to revise their study report to use original scale. However, the company in the response e0029 declined to update their study report.
    - *Reviewer comment: Use of square-root transformed numbers as the only data provided in labeling, prescribing information, synopsis, or other location is not acceptable. A comment will be sent to the applicant.*
- The second issue addressed the distinction between bleeding episodes and events. An issue was that the number of infusions was reported as identical to the number of bleeding episodes for prophylaxis and bleeding events for on-demand.
    - *Reviewer comment: This appears quite coincidental, contradicts the range for number of infusions which is given as 1-24, and may be an error. A comment will be sent to the applicant.*
- Page 2 in the response of e0029 states that the difference in transformed-scale mean and original-scale median is due to one very high ABR.
    - *Reviewer comment: A very high outlier is more likely to increase the mean more than the median, which is the opposite of the result in Table 1. A comment will be sent to the applicant.*

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

5.1 Review Strategy

- Because the current supplement contains additional clinical data and documents that were not present in the prior submission, the application was reviewed in a manner similar to a new application.

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

- See Appendix A

5.3 Table of Studies/Clinical Trials

Study No.	Objectives and Design	Inclusion Criteria	Study status	Countries
IB1001-01 [a] – PK phase (Cross-Over)	Pharmacokinetics in subjects ≥ 12 yrs; randomised, double-blind, cross-over design using marketed recombinant factor IX (BeneFIX®) as comparator; non-inferiority as assessed by $AUC_{0-\infty}$ ratio of IB1001 over BeneFIX and thrombogenic markers assessment.	Immunocompetent patients ≥ 12 years of age with severe hemophilia B and a history of frequent bleeding episodes, with at least 150 prior exposure days, adequate organ function, signed informed consent, and willingness to participate up to 12–15 months.	Complete n = 32 Including, Initial Recovery Sub-Study (n = 41) and Repeat PK Sub-Study (n = 14)	Israel, Italy, UK, USA
IB1001-01 – Treatment Phase	Safety (inhibitor development, adverse events) and efficacy (treatment of hemorrhages, annualized bleeding rate, subject and investigator assessment of efficacy) of IB1001; treatment for at least 50 exposure days; single arm, open label.	Same as above (see PK phase).	Complete 50 subjects for 50 EDs n = 68 total; 58 subjects on prophylaxis 9 subjects on on-demand, 1 unassigned n = 55 with at least 50 EDs	France, India, Israel, Italy, Poland, UK, USA
IB1001-01 – Continuation Phase	Long term safety and efficacy of IB1001;at least 50 patients up to 100 ED.	Same as above (see PK Phase).	50 subjects for 100 ED – ongoing n = 45; with at least 100 days exposure.	France, India, Israel, Italy, Poland, UK, USA
IB1001-01 – Surgical Sub-Study	To evaluate the ability of IB1001 to provide coverage against bleeding under surgical circumstances (estimated blood loss at the time of surgery and post-surgery blood loss/control of hemostasis).	Immunocompetent patients ≥ 12 years of age with severe hemophilia B and a history of frequent bleeding episodes, with at least 150 prior exposure days, adequate organ function, signed informed consent.	Completed for procedures in subjects	France, India, Israel, Italy, UK, USA

UK = United Kingdom, USA = Unites States of America.
[a] All study phases under IB1001-01 are available in one consolidated report in the **IB1001 Consolidated Report**.

[Source: 125426/0.18/e0019, *Tabular Listing*, p. 1]

5.4 Consultations

- No consultations were requested by the clinical team.

5.4.1 Advisory Committee Meeting (if applicable)

- Not applicable.

5.4.2 External Consults/Collaborations

- Not applicable.

5.5 Literature Reviewed (if applicable)

- See Appendix B.

6. Discussion of Individual Studies/Clinical Trials

All data in this report comes from Protocol IB1001-01. A search of the study report in Amendment 18, Sequence e0019 for IB1001-02 found no instances. A search of the supplemental clinical study report in Amendment 23, Sequence e0024 for IB1001-02 found no instances.

6.1 Trial IB1001-01

- Primary sources are the *Consolidated Report* in 125426/0.18/e0019 and the *Supplemental Clinical Study Report* in 125426/0.23/e0024, report dated 2014-04-15. The initial study design was:

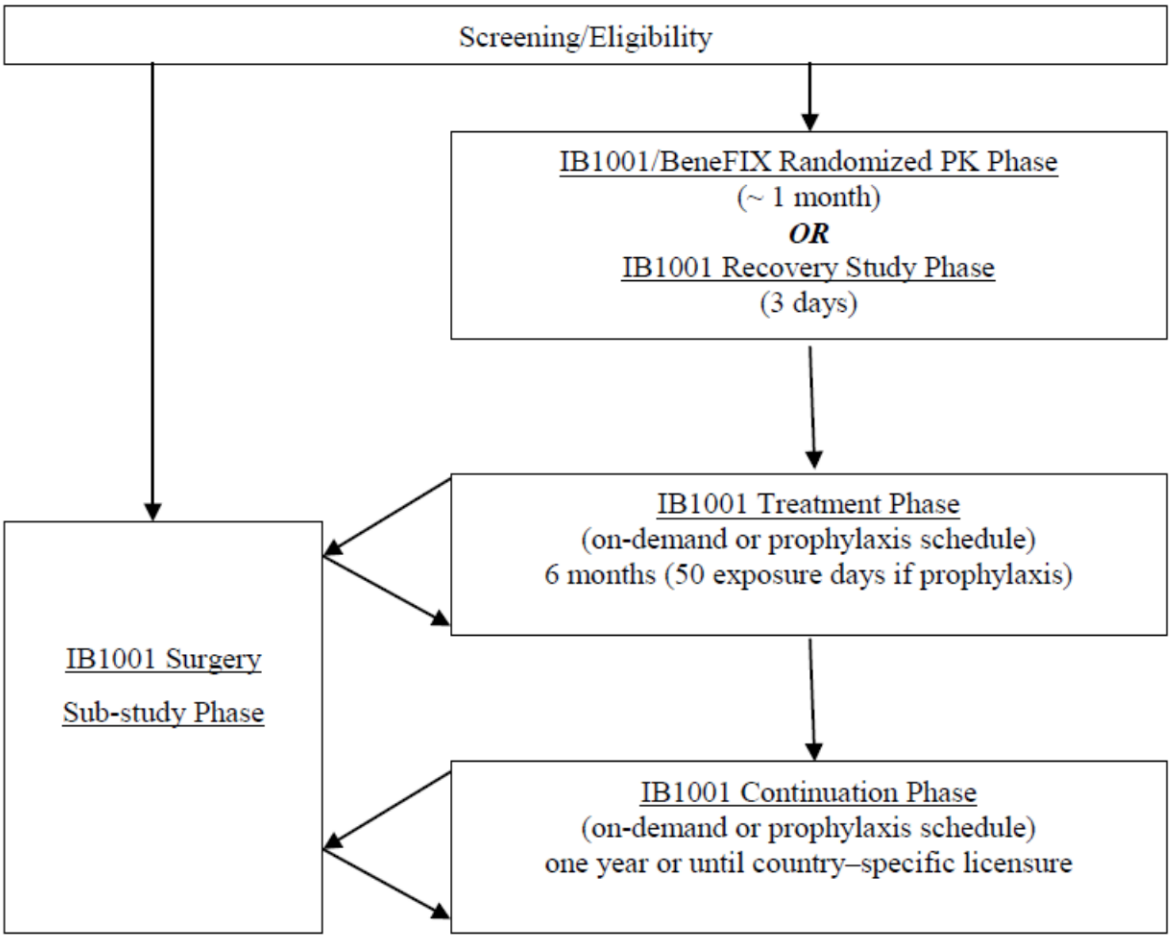


Figure 1: Overview of Study IB1001-01

[Source: BLA 125426/0.0]

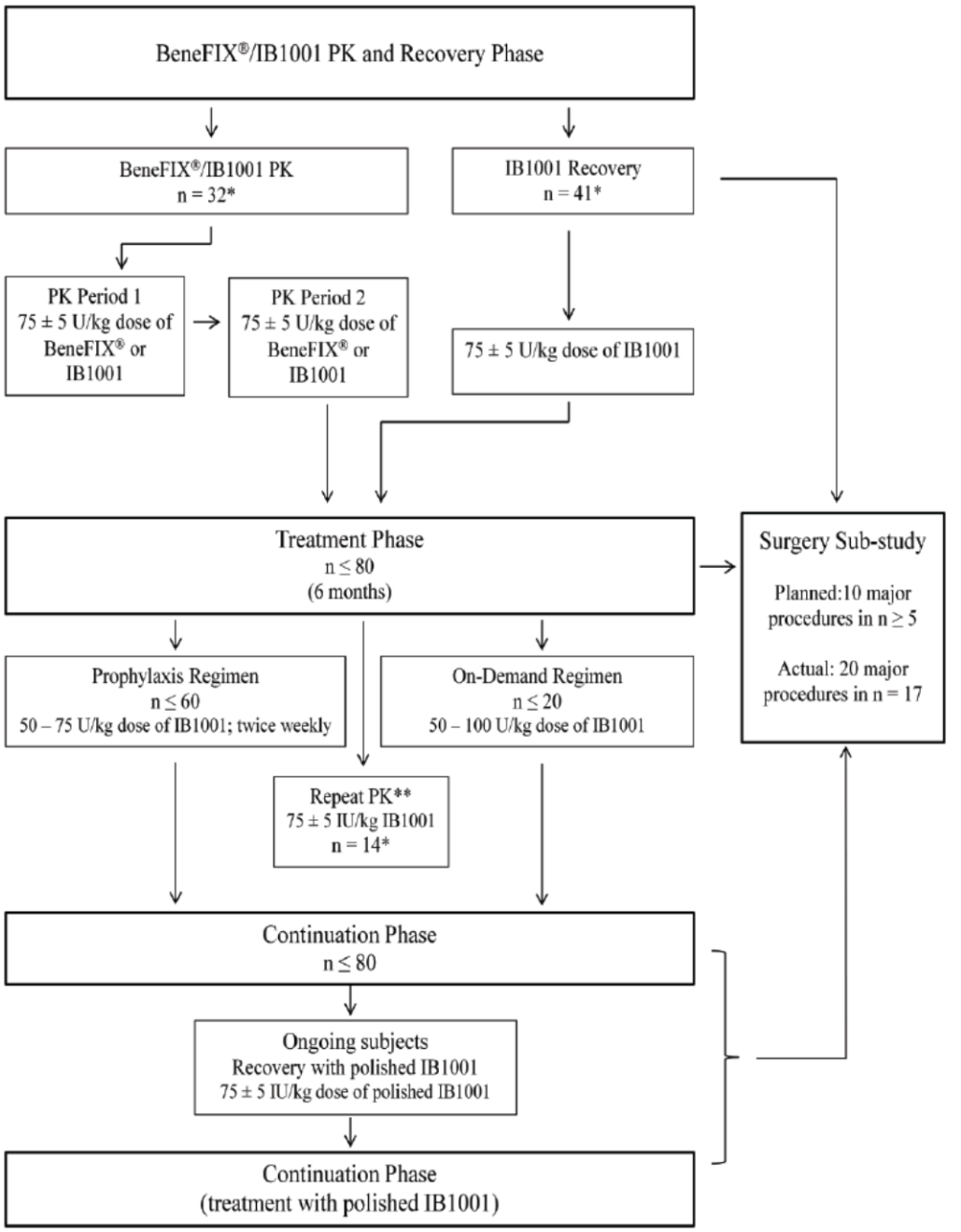
6.1.1 Objectives (Primary, Secondary, etc)

- Primary objectives of the phase 1/2/3 studies were to evaluate the safety, pharmacokinetics, and efficacy of original and modified IB-1001 for prophylaxis and on-demand treatment.
- Secondary objectives were to evaluate markers of thrombogenicity, evaluate tolerance and compliance, estimate bleeding frequency in on-demand population, evaluate efficacy for management of surgery, and gather long-term safety and efficacy data. [Source: 125426/0.18/e0019, *Report Body*, p. 20]
- For the study of mod-IB1001, objectives were to assess (1) drug recovery following a single dose, (2) anti-CHOP immunogenicity, (3) anti-FIX immunogenicity, (4) clinical safety, and (5) efficacy for prevention and control of bleeding episodes. [Source: 125426/0.23/e0024, *Supplemental Clinical Study Report*, p. 6]

6.1.2 Design Overview

- IB1001-01 was initially designed with four phases, with a fifth added later: (1) PK, (2) Treatment, (3) Continuation, (4) Surgery, and (5) Modified.

Figure 9:1 IB1001-01 Study Design



* Actual number of subjects
** Performed after 3 to 6 months of IB1001 treatment in subjects who entered Treatment Phase after completing PK Phase

[Source: 125426/0.18/e0019, *Report Body*, p. 22]

1. PK Phase: Study of BeneFIX vs. IB1001, Recovery Study, or Repeat PK Study

   - The original PK Phase was a randomized, double-blinded, crossover design. Following a ≥ 5 day washout period, levels of FIX and inhibitors were measured (schedule in 6.1.7). Subjects were randomized to BeneFIX or orig-IB1001 (regimen in 6.1.4) and crossed over after a washout period of 5-28 days. If a bleed occurred during the second washout period, the second crossover period commenced 5-28 days after the last infusion to treat the bleeding. The overall study duration for each subject was estimated at 56 days.

   - An optional repeat-IB1001 PK Phase was offered at 3-6 months after the end of the initial PK Phase. The participants received IB1001 only.

   - An IB1001 recovery assessment was required for those who did or could not participate in the PK Phase. Following a ≥ 5 day washout period of any FIX product, levels of FIX and inhibitors were assessed. IB1001 was then infused.

2. Treatment Phase: Was a non-randomized, open-label, uncontrolled study. Treatment Study lasted 6 months and was planned for approximately 50 exposure days per subject in ≥ 50 subjects. Subjects could start with prophylactic or on-demand therapy per subject and investigator preference, and could switch between regimens again as per preference. The regimens are given in 6.1.4 and monitoring in 6.1.7.

3. Continuation Phase: Optionally followed Treatment Phase and also was a non-randomized, open-label, uncontrolled study. Continuation Phase was intended to evaluate long-term safety and effectiveness for > 100 exposure days in ≥ 50 subjects. Anticipated duration was one year or up to protocol completion. Participants and investigators could again prophylactic or on-demand therapy, and switch as desired. The Continuation Phase is ongoing under protocol Amendment 11 submitted in 13551.72. Most active subjects will transition to current product (mod-IB1001) and continue in the Modified Phase.

4. Surgery Substudy: Was a non-randomized, open-label, uncontrolled study. Subjects participated in this phase for 28 days. The study was opened for enrollment 16 months after the start of the PK Phase, to allow for sufficient PK and safety data.

5. Modified Phase: Was added under Protocol Amendment 11. Subjects receive mod-IB1001 in the updated Continuation Phase for ≥ 12 months. Prior to initiation of dosing, a PK recovery study with mod-IB1001 is performed. After 12 months of Continuation Phase, participants can continue further until end of study in 2015-07.

   - For mod-IB1001, prior to receipt of study drug a recovery study is performed. After a washout period of ≥ 5 days, FIX levels are determined. The date of the mod-IB1001 recovery study is Day 0 (or Day 1) for planning subsequent visits. [Source: 125426/0.23/e0024, *Supplemental Clinical Study Report*, p. 30]

6.1.3 Population

- The study was conducted at 23 sites in 7 countries. General inclusion criteria for all phases were based on medical and hemophilia history, including baseline status: (1) hemophilia B, severe (FIX ≤ 2 IU/dL), (2) receiving on-demand therapy with ≥ 3 bleeds over past 6 months or 6 bleeds over past 12 months (annualized bleeding rate of ≥ 6), or prophylaxis therapy with bleeding pattern as above prior to

prophylaxis, and (3) previous FIX treatment ≥ 150 exposure days. Exclusion criteria included factor IX inhibitors ≥ 0.6 Bethesda Units and allergy to hamster proteins

1. PK Phase: Almost all countries required subjects be ≥ 12 years old and ≥ 40 kg body weight, except France which required subjects be ≥ 18 years old for PK. Those who did not participate in the PK Phase could still enroll into the Treatment Phase or Surgery Substudy by undergoing a PK recovery study with IB1001. Reasons for lack of PK Phase participation included small size or enrollment after closure of the PK Phase.
2. Treatment Phase: Subjects had to fulfill for general study entry criteria into the PK or Recovery Studies. In the U.S., subjects could be as young as 5 years old. In other countries, subjects had to be ≥ 12 years old. Subjects in the Treatment Study had to complete previously the PK or Recovery Study.
3. Continuation Phase: Subjects who wanted to participate in Continuation Phase had to complete the Treatment Phase.
4. Surgery Substudy: Subjects did not have to participate in other treatment phases of the trial although they did have to complete the PK Recovery Study. They could come from, or later enroll in the Treatment Phase. Surgery Substudy in all countries required in all countries required subjects be ≥ 12 years old and ≥ 40 kg body weight. Surgery cases had to be considered major and included operations for synovectomy, joint replacement or repair, total tooth extraction, intracranial hemorrhage, abdominal surgery, prostatectomy, or repair of major muscular bleeds. No subjects have undergone surgery with mod-IB1001.
5. Continuation Phase study of mod-IB1001: [Source: 125426/0.23, e0024, Supplemental Clinical Study Report]

    - Data was collected from 2013-10 through 2014-02. A total of 17 subjects had received mod-IB1001 as of the cover letter of 2014-04-22, 11 under IB1001-01 and 6 under IB1001-02. Data lock for this submission was 2014-02-28 and includes PK, immunogenicity, and safety data for 7 subjects in IB1001-01. Monitoring of other subjects is ongoing.
    - Inclusion criteria were similar to the original criteria in Amendment 18, Serial e0019 except:
        - Upper limit of liver function increased to 2 times the upper limit of normal range for ALT and AST, from 1.5 times.
        - Minimum weight to participate in any PK study or the Surgery Substudy increased to 50 kg, from 40 kg.
        - Added hemoglobin ≥ 7 gm/dL at the time of the blood draw and total bilirubin ≤ 1.5 times the upper limit of normal range, were not specified previously in e0019.
    - Exclusion criteria were similar to the original criteria in Amendment 18, Serial e0019 except the following which were added and not specified previously in e0019:
        - Known allergic reaction to hamster proteins
        - On medications that could impact hemostasis, such as aspirin
        - Hypersensitivity to the active substance or any excipients

- Concomitant Medications: During the study, subjects may not take aspirin or other drugs that impact hemostasis, immunosuppressives, or other factor IX products except when permitted because of regulatory matters.

6.1.4 Study Treatments or Agents Mandated by the Protocol

1. PK Phase: In this crossover trial, participants received a single intravenous dose of 75 ± 5 IU/kg of either IB1001 or BeneFIX, and then crossed over. Participants in the recovery study received a single intravenous dose of 75 ± 5 IU/kg of IB1001.
2. Treatment Phase: With orig-IB1001, the initial prophylaxis dose was 50 - 75 IU/kg twice weekly. Twice weekly could be spaced as far as 4 days apart. Bleeding episodes were treated with an initial intravenous dose of 50-100 IU/kg of IB1001. Repeat doses could be administered as needed to achieve hemostasis. For prophylaxis, the actual mean dose per infusion was 4225 IU or 55 IU/kg (median 53 IU/kg, range 26-80 IU/kg). For on-demand treatment, mean dose per infusion was 4674 IU (median 59 IU/kg, range 24-94 IU/kg). [Source: 125426/0.18/e0019, *Summary of Clinical Efficacy*, p. 14]
3. Continuation Phase: Treatments were the same as Treatment Phase.
4. Surgery Substudy: Bolus or continuous infusion of IB1001 was permitted. Bolus treatment was ≤ 120 IU/kg within 1 hour of surgery, followed by bolus dosing cumulatively totaling 60 IU/kg at 12 hours and 120 IU/kg at 24 hours. Dosing was every 12 hours for ≥ 3 days and thereafter for as long as necessary. Continuous infusion was titrated to maintain FIX levels between 70 - 110% for ≥ 3 days after surgery.
5. Modified Phase: The dose for the required recovery study was 75 IU/kg of mod-IB1001. No comparator was dosed. Dosing regiments for Continuation Phase with mod-iB1001 were 50-75 IU/kg for prophylaxis and 50 IU/kg for on-demand. For Surgery Substudy during this phase [there have been no enrollees, so far], a bolus of 120 IU/kg would be given 1 hour before surgery, 60 IU/kg 12 hours after surgery, with subsequent infusions to maintain a target range of 70-110% for ≥ 3 days after surgery.

6.1.6 Sites and Centers

- The original IB1001 studies were performed at 23 sites in 7 countries: U.S.A, U.K., France, Italy, Israel, Poland, and, India. Six sites in the U.S. and U.K. contributed data for seven subjects transitioned to mod-IB1001 for the supplemental report.

6.1.7 Surveillance/Monitoring

- A data safety monitoring board has been monitoring the clinical trial for the entire existence of the trial.

1. PK Phase: FIX levels were measured preinfusion and postinfusion at 30 minutes and hours 1, 3, 6, 9, 12, 24, 36, 48, 60, and 72. Thrombogenic markers included D-dimer, F1+2, and TAT and were measured preinfusion and postinfusion at hours 3 and 24. The measurements in the optional repeat PK study were identical. For subjects who

had a recovery study only, FIX levels were measured at 15 minutes and hours 1 and 24.

2. Treatment Phase: The frequency of breakthrough bleeding during prophylaxis or spontaneous bleeding during on-demand was monitored. Adverse events, tolerance, and compliance were monitored with subject-reported diaries. In the prophylaxis group, inhibitory (neutralizing) and non-inhibitory antibodies were measured at months 3 and 6. Antibodies against CHOP were measured at 3-month intervals. In the on-demand group, the same measurements were made after the first infusion, with the same timing.

3. Continuation Phase: Orig-IB1001 was studied before and after the reporting of immunogenicity and release of clinical hold (pre-report vs. post-report). Subjects were monitored for up to 39 months [Source: 125426/0.18/e0019, *Report Body*, p. 84]

    - In Continuation Phase pre-report, antibodies inhibitory, noninhibitory, and anti-CHOP were measured every 3 months along with safety and efficacy data. Measurements of anti-CHOP were more frequent after conversion to positive. Recovery of FIX was performed every 6 months after Protocol Amendment 10 submitted in 2012 under IND 13551.59.

    - For subjects who continued on orig-IB1001 post-report in U.K. or India, with or without interruption, immunogenicity monitoring every 3 months includes safety testing for anti-FIX antibodies inhibitory and noninhibitory, and anti-CHOP antibodies; and efficacy assessments.

    - For subjects transitioned from orig-IB1001 to marketed product who remained on marketed product in the U.S. or India, immunogenicity monitoring is performed every 3 months as above. Efficacy testing was not continued. [Source: 125426/0.23/e0024, *Supplemental Clinical Study Report*, p. 28]

4. Surgery Substudy: FIX levels were before every infusion and 5-30 minutes postinfusion. Antibodies inhibitory, noninhibitory, and anti-CHOP were measured immediately preoperatively and once 7 - 28 days post discontinuation of IB1001 treatment. Vital signs were monitored routinely and additionally appropriate to the amount of bleeding.

5. Modified Phase:

    - For PK of mod-IB1001, recovery was the only parameter investigated. This is performed at transition and every 6 months thereafter. [Source: 125426/0.23/e0024, *Supplemental Clinical Study Report*, p. 43]

    - In mod-IB1001 Continuation Phase:

        - Efficacy is calculated from data collected in subject diaries about breakthrough or spontaneous bleeding. Investigators also rate the efficacy of treatment. Quality-of-life assessments are made at the beginning of Continuation Phase and at months 6 and 12 of mod-IB1001 treatment.

        - The safety monitoring includes clinical safety, laboratory findings, and immunogenicity results. Immunogenicity testing included antibodies against CHOP and is performed every 3 months [Source: 125426/0.23/e0024, *Supplemental Clinical Study Report*, p. 28].

- The schedule of assessments for mod-IB1001 in Continuation Phase is provided in Appendix E. End-of-study assessment, either completion or withdrawal, is given on page 34 of the study report.
- During first 12 months of treatment with mod-IB1001, assessments are every 3 months. Those who choose to continue ≥ 12 months until 2015-07 are assessed every 6 months.

- Table of Assessments for mod-IB1001 Continuation Phase:

Table 9-2 Schedule of Evaluations for Treatment with Polished IB1001 in Continuation Phase

	Continuation Phase – 12 months of treatment with polished IB1001[¶]					
	Day 0[*]	Assessments[**] at 5 ED, 1 and 2 months (± 7 days)	3-month Visit (±2 weeks)[***]	6-month Visit (±2 weeks)[***]	9-month Visit (±2 weeks)[***]	12-month Visit (±2 weeks)[***]
Health status and QoL[a]	X			X		X
Medical history	X		X	X	X	X
Vital signs	X		X	X	X	X
Physical exam	X		X	X	X	X
Adverse events	X		X	X	X	X
Concomitant medications	X		X	X	X	X
Blood chemistries[b]	X		X	X	X	X
CBC with differential	X		X	X	X	X
Urinalysis	X		X	X	X	X
Inhibitor titer	X	X	X	X	X	X
Non-inhibitory antibodies	X	X	X	X	X	X
anti-CHOP antibodies	X	X	X	X	X	X
Polished IB1001 Recovery[¥]	X[¥]			X		X
Subject diary:	X	X	X	X	X	X
Infusions	X	X	X	X	X	X
Bleeding summary	X	X	X	X	X	X
Efficacy assessment	X	X	X	X	X	X
Adverse events and concomitant medications	X	X	X	X	X	X
Compliance	X		X	X	X	X

[a] Quality of Life assessments: performed at the beginning of Continuation Phase for subjects ≥12 years of age.
[b] Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), blood urea nitrogen (BUN), uric acid, creatinine, total bilirubin and glucose.

[Source: 125426/0.23/e0024, *Supplemental Clinical Study Report*, p. 32]

- End-of-study Assessments:

Table 9-3 Schedule of Evaluations for End of Study or Early Termination

End of Study or Early Termination	
Evaluations	**EOS/early termination**
Health status and QoL[a]	X
Vital signs	X
Physical exam	X
Medical history	X
Adverse events	X
Concomitant medications	X
Blood chemistries [b]	X
hs-CRP	X
CBC with differential	X
Urinalysis	X
Inhibitor titer	X
Non-inhibitory antibodies	X
anti-CHOP antibodies	X
Subject diary:	X
Infusions	X
Bleeding summary	X
Efficacy assessment	X
Adverse events and concomitant medications	X
Compliance	X
Recovery study [c]	X[d]

[a] Quality of life assessments should be done at the beginning of the study visit, and will be assessed for subjects who are at least 12 years of age.
[b] Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), blood urea nitrogen (BUN), uric acid, creatinine, total bilirubin, and glucose.
[c] Factor IX levels pre-infusion and 30 and 60 minutes post-infusion.
[d] Assessed during early termination; recovery will be evaluated if lack of efficacy is reason for withdrawal.

[Source: 125426/0.23/e0024, *Supplemental Clinical Study Report*, p. 34]

- For Study IB1001-02, anti-CHOP monitoring was added.

6.1.8 Endpoints and Criteria for Study Success

1. PK Phase: Pharmacokinetic endpoints included C(max), AUC to 72 hours and total, clearance, rate of elimination for terminal phase, terminal half-life, in vivo recovery, incremental recovery, mean residence time, and volume of distribution at steady state. Recovery of factor IX in the initial recovery study is calculated as C(max) minus baseline levels.
2. Treatment Phase: Tolerance and compliance were assessed from subject-reported diaries. Efficacy endpoints for bleeding episodes were defined for prophylaxis and on-demand treatment separately. If subjects switched regimens, separate rates were calculated for each regimen. Endpoints will be generated for (1) subjects who complete ≥ 50 exposure days (ED), (2) subjects who complete ≥ 100 ED, and all subjects in the intent-to-treat population. For overall efficacy in subjects who switched regimens, efficacy was assigned to the regimen the subject was on at the time of endpoint assessment.

    - For prophylaxis, safety endpoints included product tolerance, adverse events, and immunogenicity. Events within 72 hours of infusion were collected. For

prophylaxis, the efficacy endpoint was the annualized bleeding rate for breakthrough bleeding.

  - Amendment 125426/0.28/e0029, *Response*, clarifies the distinction between bleeding episodes and bleeding events. Number of bleeds is to be interpreted as bleeding events. A bleeding episode may have more than one bleeding event. A bleeding episode could include bleeding events involving different joints, if they occur within a 24-hour time period.

- For treatment of bleeding episodes in the prophylactic and on-demand groups, clinical endpoints gathered from subjects and investigators were used. These included (1) subject's rating of efficacy, (2) investigator's rating of efficacy, (3) change in pain, (4) change in swelling, (5) time to cessation, and (6) number of infusions required. Quality of life measurements are made using the EQ-5D in subjects ≥ 12 years old [Source: 125426/0.18, e0019, Synopsis, pp. 4-5, 7, 13]. Grading of efficacy followed the following criteria:
  - Excellent: Dramatic response
  - Good: Required an additional infusion for resolution
  - Fair: Probable response requiring several additional infusions
  - Poor: No improvement

3. Continuation Phase: Was conducted in identical fashion to Treatment Phase.

5. Modified Phase: Safety endpoints include clinical safety, laboratory findings, and immunogenicity results. Adverse events were analyzed by number of events, number of subjects, and percentage of subjects. Efficacy endpoints generated from subject diaries were annualized bleed rate (ABR) and degree of hemorrhagic control for breakthrough and spontaneous bleeding episodes. Degree of hemorrhage control was aggregated from subject's rating of efficacy, change in pain or swelling during episode, time and number of infusions to cessation of bleeding. Investigator's rating of efficacy is collected.

   a. PK evaluation for mod-IB1001 assessed recovery only. After a washout period of ≥ 5 days, FIX levels are determined preinfusion, and following a single intravenous infusion of 75 IU/kg of mod-IB1001 postinfusion at 15 minutes and hours 1 and 24. For mod-IB1001, recovery was calculated as C(max) - baseline FIX. [Source: 125426/0.23/e0024, *Supplemental Clinical Study Report*, p. 30]

   b. Definitions for immunogenicity are given in Section 6.1.12.1.

6.1.9 Statistical Considerations & Statistical Analysis Plan

- Sample Sizes

1. PK Phase: The planned sample size was to enroll 34 participants with the goal of having 28 evaluable subjects:

2. Treatment Phase: The planned sample size was for ≤ 80 subjects overall. A subset of 60 participants on prophylaxis were planned in order to have 50 evaluable subjects. Similarly, a second plan was to enroll 20 participants for on-demand treatment in order to have 18 evaluate subjects.

3. Continuation Phase: The goal was to gather data out to at least 100 exposure days in ≥50 subjects.
4. Surgery Substudy: The plan was to enroll ≥ 5 subjects with the goal of collecting 10 surgical cases.
5. Modified Phase: No specific sample size was planned.

- Statistical Methods
  - Analyses of safety across the phases looked at event counts, and subject counts and percentages.

1. PK Phase: Efficacy was analyzed with comparison of AUC performed using calculation of a one-sided 95% confidence interval. Noninferiority is declared if the lower bound of the interval falls above 80%. Similar analysis is performed for AUC to 72 hours and C(max). Other efficacy analyses will use descriptive statistics without formal testing. Safety used descriptive summaries and descriptive comparisons between the two treatments.
2. Treatment Phase: Efficacy was analyzed using descriptive summaries generated for all efficacy endpoints. Median rates and 95% confidence intervals of the mean and interquartile ranges will be calculated. Mean numbers of bleeding episodes for prophylaxis vs. on-demand will be compared using a two-sample t-test for two Poisson means. Safety analyses of adverse events used descriptive statistics, with Treatment and Continuation Phases combined.
    a. ABR was calculated as (number of bleeds x 12) ÷ (number of months of observation).
3. Continuation Phase: This will be combined with Treatment Phase.
4. Surgery Substudy: This will be analyzed descriptively for surgery endpoints.
5. Modified Phase: For mod-IB1001, descriptive summaries and listings are provided for all efficacy endpoints. Median rates, 95% confidence intervals of the mean, and interquartile ranges are computed. Mean number of bleeding episodes per subject will be compared between prophylaxis and on-demand populations using a two-sample t-test for the comparison of two Poisson means. Analysis of adverse event endpoints includes descriptive statistics and summaries.
    a. PK recovery data are listed and summarized. Recovery data for original IB1001 are also listed for subjects who receive mod-IB1001.

6.1.10 Study Population and Disposition

- A total of 92 subjects provided consent to screen for IB1001. [Source: 125426/0.18/e0019, *Summary of Clinical Safety*, p.13]. A total of 77 subjects were ultimately enrolled in the Phase 1/2/3 clinical trial. Enrollment of new subjects was closed 2011-05 and has remained closed. Some parts of the clinical trial have been completed (PK or Recovery Phase, Treatment Phase, Surgery Substudy). The Continuation Phase is ongoing, under which subjects transition to modified IB1001.
- All data in the original resubmission, 125426/0.18/e0019 with data lock of 2013-03, are with the product before the additional (b) (4) was

added. No subjects had been transitioned to the current version of the product at that time. Safety and efficacy were determined during clinical trials using original IB1001. Extensive comparability and nonclinical testing were done and showed that the original and modified products were equivalent other than removal of host cell proteins. Based on the results, efficacy was extrapolated from original IB1001 to modified IB1001 (mod-IB1001). A *Supplemental Clinical Study Report* dated 2014-02-28 provided data on seven subjects who had transitioned. The data for the supplemental report was from 2013-10 through 2014-02. A communication dated 2012-04-22 stated that 17 subjects had been transitioned to mod-IB1001. These include three subjects in the U.S. and eight subjects in the U.K. under Study IB1001-01, and six subjects in India under IB1001-02. Aside from this demographic data, no additional data were provided.

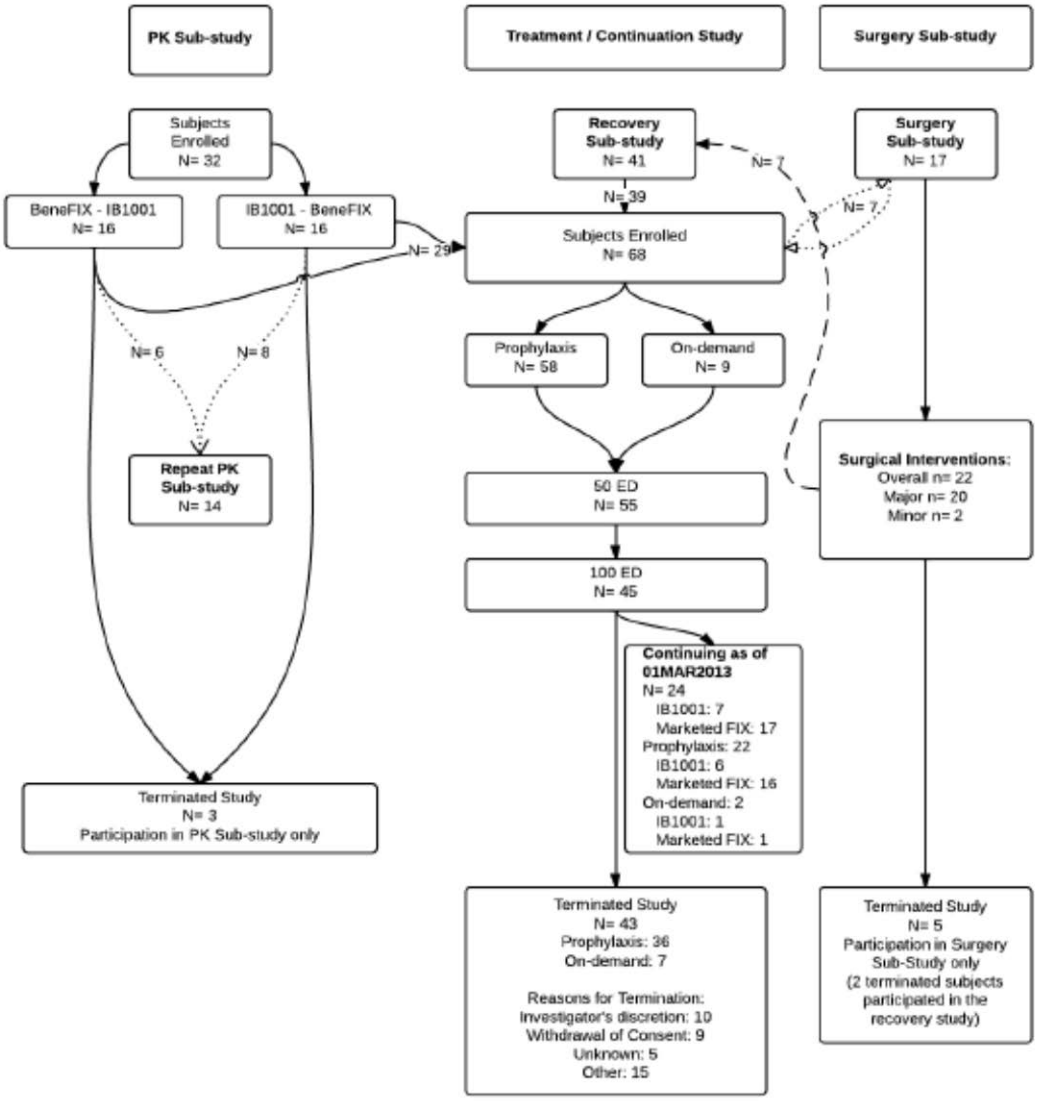
- As of 125426/0.18/e0019 with data lock of 2013-03, 24 subjects agreed to remain in Continuation Phase with the eventual goal to transition to mod-IB1001. Of the 24 subjects, 17 subjects transitioned to marketed product and 7 subjects stayed on orig-IB1001 [presumably due to availability and cost of marketed product outside the U.S.]. As of 125426/0.23/e0024 with data lock of 2014-02-28, seven subjects had transitioned to mod-IB1001. [Source: 125426/0.23/e0024, *Supplemental Clinical Study Report,* p.47]

1. The mod-IB1001Continuation Phase and the study as a whole will end 2015-07. Pharmacokinetic Phase: After 32 subjects were enrolled, it was determined that they were all evaluable. Once the PK study was completed, these subjects were eligible to proceed to other phases of the trial such as Surgery Substudy or Treatment Phase
2. Treatment Phase: The plan was to enroll ≤ 80 subjects overall with 60 in prophylaxis and 20 on demand, for 50 evaluable prophylaxis and 18 evaluable on-demand subjects. Eight other subjects were in other phases but did not continue with Treatment Phase (three in PK and five in Surgery). The cohort started with PK Phase (n = 29) or recovery study (n = 41).
    - In 2012-05, a higher than expected number of subjects were found to have developed high anti-CHOP antibody titers. Subjects with high titers stopped treatment with IB1001, and monitoring continued for those willing to stay on study while being treated with another marketed product.
    - In 2012-07, the study was placed on clinical hold in the U.S. and all participants stopped treatment with IB1001. Subjects either exited the study or stayed on study with transition to a marketed FIX product. [Source: 125426/0.23/e0024, *Supplemental Clinical Study Report,* p. 28]
    - Disposition in other countries is briefly discussed in 2.6.
3. Continuation Phase: Subjects were allowed to stay in Continuation Phase as desired. Clinical hold was removed on 2013-07-26. As of data lock date of 2014-02-28 for the *Supplemental Clinical Study Report*, 24 subjects remained in the Continuation Phase.
4. Surgery Substudy: The study planned to enroll ≥ 5 subjects and collect ≥ 10 major surgeries. There was a provision in the modified protocol to collect more surgery subjects. Five subjects exited the study after their surgery. Seven subjects came to Surgery Substudy from Treatment Phase. Five subjects entered Treatment Phase after surgery.

5. Modified Phase:
    - The ITT population for mod-IB1001 consists of subjects who received at least dose of mod-IB1001. As of the date of the report in Amendment 0.18/e0019, 2014-01-17, no subjects had transitioned to mod-IB1001, so none were included in that report.
    - Supplemental clinical study report with data cutoff of 2014-02-28 describes data from 7 subjects. Cover letter from Sequence e0024 dated 2014-04-22 states that, as of that date, "17 subjects have transitioned onto" mod-IB1001.
    - The *Pediatric Deferral Request* submitted 2014-06-17 in e0033 states "Out of 17 ongoing subjects [in IB1001-01] (including one child < 12 years and 3 adolescent patients), 12 have transitioned to polished product and five subjects await transition."

Disposition Chart [Source: 125426/0.18/e0019, *Report Body*, p.60]

Figure 10:1 Subject Disposition for Study IB1001-01



6.1.10.1 Populations Enrolled/Analyzed

- A total of 77 subjects were enrolled in the Phase 1/2/3 clinical trial. Table 12 in 125426/0.18/e0019, *Summary of Clinical Efficacy*, p. 28, provides addition details on subject disposition. Estimated bleeds in the 6 months prior to enrollment are given in the following table:

Table: Summary of Estimated Bleeds in the 6 Months Prior to Enrollment

		n = 76 [a]
Number of Bleeds in the Last 6 Months	n	66
	Mean	2.7
	Std Dev	3.58
	Median	1.0
	Minimum	0
	Maximum	20
Percent of Bleeding Episodes Caused by Injury [n (%)]	100%	11 (18.3%)
	70–99%	3 (5.0%)
	30–69%	15 (25.0%)
	1–29%	11 (18.3%)
	0%	20 (33.3%)

[a] Subject (b) (6) is excluded from the summary because she was a mild hemophilia patient included in the study with a waiver.

[Source: 125426/0.18/e0019, *Report Body*, Table 11:2, p.66]

1. PK Phase: After 32 subjects were enrolled (plan was 34 to have 28 evaluable), it was determined that they were all evaluable. Since the desired sample size was 28 subjects, the PK Phase was closed to enrollment. A subset of 14 subjects participated in the repeat PK study. Mean age was 33 years. No subjects < 12 years old were enrolled. Three subjects participated in the PK study only.
2. Treatment Phase: Overall, 68 subjects enrolled into the treatment phase. There were 57 subjects enrolled in the Treatment Study who were preassigned to receive prophylaxis and 9 preassigned to receive on-demand. Mean age was 30 years. Pharmacokinetic entry data came from the PK Study or a recovery study in 29 and 39 subjects, respectively. Seven subjects came from the Surgery Substudy. Ultimately, 58 subjects received prophylaxis. Because subjects could switch regimens, over the length of investigation 61 subjects received prophylaxis and 12 received on-demand. A total of 9395 exposure days were experienced by the 68 subjects, with 58 subjects on prophylaxis having mean exposure of 149 days (median 136) and length of study of 18 months (range 2-40 months). Mean exposure for nine subjects preassigned to on-demand treatment was 84 days (median 94 days) and length of study of 16 months (range 2-37 months) [Sources: 125426/0.23/e0024, *Supplemental Clinical Study Report*, p. 7]. A subset of 55 subjects had reached 50 exposure days by the data cutoff date of 2013-03 and are included in the ITT population [Source: 125426/0.32, e0033, *Deferral Request*, p. 3]. Only 9 evaluable subjects were in the on-demand group, fewer than the desired 18 subjects.
3. Continuation Phase: As of data lock date of 2013-03-01, 45 of 68 subjects had reached ≥ 100 exposure days for determination of long-term safety and efficacy [Sources: 125426/0.32, e0033, *Deferral Request*, p. 3; 125426/0.18, e0019, *Report Body*, Section 11.1..3, p. 63]. As of data lock date of 2014-02-28 for the *Supplemental Clinical Study Report*, 24 subjects remained active in the Continuation Phase.
4. Surgery Substudy: By 2013-03, 17 subjects (five planned) were enrolled and 20 major surgery cases (10 planned) were collected. Mean age was 33 years.

There was one subject who enrolled in the Substudy but improved was surgery was cancelled. This person was included in the analysis of safety. No subjects have undergone a surgical procedure with mod-IB1001. Continuous infusion was used in six procedures and bolus in 13 procedures. Five subjects participated in the Surgery Substudy only.

- The applicant has combined FDA-defined pediatric subjects (< 16) with all subjects < 18 years old. These subjects contributed to analyses of PK, safety, and efficacy as shown in the table below. Included in the pivotal clinical trial were twelve subjects ≤ 18 years old, including eight subjects < 16 and six between 12 and < 16 years. Nine subjects between 7 and 17 years have ≥ 100 exposure days.

Table. PTPs from Study IB1001-01 Less than 18 Years of Age

Patient ID	Age (years	Data Contribution to Study IB1001-01 Analyses	Total Exposure Days
(b) (6)	17	PK, safety, efficacy	188
	14	PK, safety, efficacy	221
	17	PK, safety, efficacy	211
	16	PK, safety, efficacy	171
	10	Safety, efficacy	267
	14	Safety, efficacy	67
	12	Safety, efficacy	49
	10	Safety, efficacy	125
	7	Safety, efficacy	123
	14	Safety	1
	14	Safety, efficacy, surgery	141
	12	Safety, efficacy, surgery	138

[Source: Adapted from 125426/0.32, e0033, *Deferral Request*, p. 4]

- Modified Phase: For mod-IB1001, the original supplemental report in e0024 reported on seven subjects. Amendment 26 in e0027 described an additional five subjects transitioned to mod-IB1001 and another five in India eligible to transition pending regulatory approval. [Response, p. 1]
    - The seven subjects are 7 males, age range of 24-57 years, median 31 years old. Four of the subjects transitioned from orig-IB1001 and three transitioned from commercial products.
- As of 2014-06-17, Study IB1001-02 has enrolled nine subjects including three subjects < 6 (aged 2, 4, 4) and six subjects between 6 and 12, inclusive (aged 7, 9, 10, 10, 11). [Source: 125426/0.32, e0033, *Deferral Request*, p. 5]

6.1.10.1.1 Demographics

- Table 13 in 125426/0.18/e0019, *Summary of Clinical Efficacy*, p. 33, provides addition details on subject demographics.

6.1.11 Efficacy Analyses

Efficacy analysis includes data from 2009-02 to 2013-03. The original proposal included studies for prophylaxis and on-demand treatment. Efficacy endpoints are generated from subject diaries of bleeding episodes, either breakthrough or spontaneous. Clinical endpoints included annualized bleeding rate or degree of hemorrhage control. Annualized bleeding rates were evaluated for subjects in prophylaxis and on-demand groups. Degree of hemorrhage control is gathered from the subject's rating of efficacy, change in pain or swelling during episode, time and number of infusions to cessation of bleeding. Investigator's rating of efficacy is collected. [Source: 125426/0.18/e0019, *Report Body*, p.34]

Efficacy is reported for prophylaxis, treatment of breakthrough bleeding events, on-demand treatment, and treatment of bleeding during on-demand treatment (episodic).

6.1.11.1 Analyses of Primary Endpoint(s)

1. PK Phase: IB1001 and BeneFIX had similar PK profiles. No significant differences were identified in AUC to 72 hours or total, C(max), clearance, elimination rate, terminal half-life, in vivo recovery, volume of distribution, mean residence time, or incremental recovery. Factor concentrations in the PK Study and initial Recovery Study were consistent.

Summary of PK Parameters – BeneFIX® vs. IB1001

PK Parameter*	BeneFIX® Mean ± SD	IB1001 Mean ± SD
$AUC_{0-\infty}$ (IU*hr/dL)	1656.48 ± 468.61	1572.51 ± 451.50
AUC_{0-72} (IU*hr/dL)	1414.35 ± 339.39	1374.64 ± 356.36
C_{max} (IU/dL)	72.81 ± 17.50	73.72 ± 16.57
CL (dL/kg*hr)	0.050 ± 0.012	0.051 ± 0.013
$t_{1/2}$ (hr)	26.38 ± 13.60	24.23 ± 6.91
Incremental recovery (IU/dL:IU/kg)	0.94 ± 0.23	0.98 ± 0.21

*PK parameters calculated using the actual dose.

[Source: 125426/0.18/e0019, *Report Body*, Table 11:22, p. 96]

PK Phase, Repeat: Pharmacokinetic profiles with IB1001 were stable when repeated and reassessed after 6 months. [Source: 125426/0.18/e0019, *Report Body*, p. 76]

2. Treatment Phase: The ITT population consisted of subjects with severe hemophilia B (factor IX levels ≤ 2%), aged 7-64 years, with ≥ 150 exposure days, most with bleeds in ≥ 2 major joints. Analyses were performed on the ITT population.

Table. Efficacy of IXINITY in Treatment Phase

	Prophylaxis (n = 61)	**On-Demand (n = 12)**

Dose per Infusion (IU/kg) Mean (± SD) Median (range)	 55 (± 13) 53 (± 26-80)	 60 (± 18) 59 (24-94)
Total ABR Median (range) **Square-Root Transformed ABR** Mean (± SD)	 1.5 (0.0-47.5) 1.3 (± 1.3)	 16.0 (0.0-39.4) 3.6 (± 2.0)
Patients with zero bleeding episodes	19 (31%)	2 (17%)

[Source: Adapted from *Draft Package Insert*, Amendment 26, Table 6; Adapted from 125426/0.28/e0029, *Response*, p. 2]

Also, **Table. Summary of Annualized Bleeding Rate**

Table 11:12 Summary of Annualized Bleed Rate

	Prophylaxis	On-Demand	Overall
n	61	12	65
Mean	1.33	3.55	1.65
Standard Deviation	1.35	1.97	1.54
95% CI	(0.99, 1.67)	(2.29, 4.80)	(1.27, 2.03)

Annualized Bleed Rate = square-root transformed calculation

[Source: 125426/0.18/e0019, *Report Body*, Table 11:12, p. 83]

Using the definitions of bleeding episodes and bleeding events given in Section 6.1.8, the absolute numbers in the following table were generated upon re-review, prompted in part from an information request dated 2014-05-22.

Table. Bleeding Episodes versus Bleeding Events

	Prophylaxis (n = 61	On-demand (n = 12)
Total Bleeding Events	303	227
Total Bleeding Episodes	286	222

[Source: Adapted from 125426/0.28/e0029, *Response*, p. 3]

The *Response*, p. 3, states that 286 infusions were made in 286 bleeding episodes in the prophylaxis group, and that 227 infusions were made in 227 bleeding events in the on-demand group.

Reviewer comment: Square-root transformed means will not be acceptable for presenting mean results in results and are only acceptable for use in statistical calculations.

Reviewer comment: *It does seem coincidental that the number of infusions matches the number of events or episodes, and is inconsistent with the range of infusions from 1-24 on page 237 of the study report. A comment for clarification was prepared.*

a. Prophylaxis: The square-root transformed, mean annualized bleeding rate (ABR) under prophylaxis was 1.33 ± 1.35 (95% CI 0.99-1.68) [Source: 125426/0.18/e0019, *Report Body*, p. 83]. Investigators rated the efficacy of prophylaxis in no subject as "not effective," 3-8% as partially effective, and 78-100% as effective. The square-root transformed ABR was significantly lower in the prophylaxis group (3.55 vs. 1.33, $p < 0.001$).

Seven subjects on prophylaxis had > 10 bleeding episodes; in some, most were post-traumatic. One subject (b) (6) experienced 35 bleeding episodes, 32 which were post-traumatic. There were others with a similar pattern. Breakthrough bleeding (spontaneous plus post-traumatic) occurred in 69% of subjects on prophylaxis (n = 42 subjects), totaling 286 bleeding episodes [286 / 42 = 7 bleeding episodes per subject with bleeds]. Treatment of bleeds required 1.9 ± 2.2 infusions (median 1 infusion, range: 1–20). Bleeds resolved after one or two infusions in 37% (n = 189) or 8% (n = 41), respectively. Only 4% (n = 20) required ≥ 5 infusions and the maximum was 20 infusions. Most of the bleeding episodes that required many infusions were related to surgery [presumably minor or not Surgery Substudy], trauma, target joints, and/or muscle bleeds. Subjects rated the efficacy of treatment for breakthrough bleeds as excellent, good, fair, or poor in 51%, 32%, 12%, or 4%, respectively.

Reviewer comment: *The number 37% for number of infusions needed is likely an error reported in the Summary of Clinical Efficacy, and we calculate closer to 70%. A comment is included for clarification.*

ABR for different etiologies of bleeding during prophylaxis are given in the table below:

Table: Annualized Bleeding Rate by Cause - Prophylaxis

	Treatment Regimen		
	Prophylaxis		
	Trauma	Spontaneous	Unknown
n	61	61	61
Minimum	0.00	0.00	0.00
25th percentile	0.00	0.00	0.00
Median	0.00	0.00	0.00
75th percentile	2.43	1.22	0.63
Maximum	43.61	23.82	2.99

[Source: 125426/0.18/e0019, *Report Body*, Table 11:13, p. 84]

Reviewer comment: *Square-root transformed means will not be acceptable for presenting mean results in results and are only acceptable for use in statistical calculations.*

On-Demand: The median number of bleeding episodes was 16 per year (range 0-39) [Source: 125426/0.18/e0019, *Report Body*, p. 85]. The square-root transformed, mean annualized ABR for on-demand treatment was 3.55 ± 1.97 (95% CI 2.29-4.80). IB1001 was effective for treatment of bleeding episodes as assessed by times for resolution of the bleed, associated pain, and swelling. Investigators ranked one subject's treatment as partially effective (12.5% of subjects), and all other treatments were ranked as effective in 75-100% of subjects. Subjects in the on-demand group rated the efficacy of treatment for spontaneous bleeds as excellent or good in 24% and 56%, respectively. Number of infusions required to treat spontaneous bleeds averaged 1.6 ± 1.8 infusions. [Source: 125426/0.18/e0019, *Report Body*, p. 86]

ABR for different etiologies of bleeding during prophylaxis are given in the table below:

Table: Annualized Bleeding Rate by Cause - On-Demand

Treatment Regimen	On-Demand		
	Trauma	Spontaneous	Unknown
n	12	12	12
Minimum	0.00	0.00	0.00
25th percentile	0.00	1.89	0.00
Median	2.67	7.49	0.00
75th percentile	3.96	21.32	1.44
Maximum	7.09	39.66	11.99

[Source: 125426/0.18/e0019, *Report Body*, Table 11:15, p. 85]

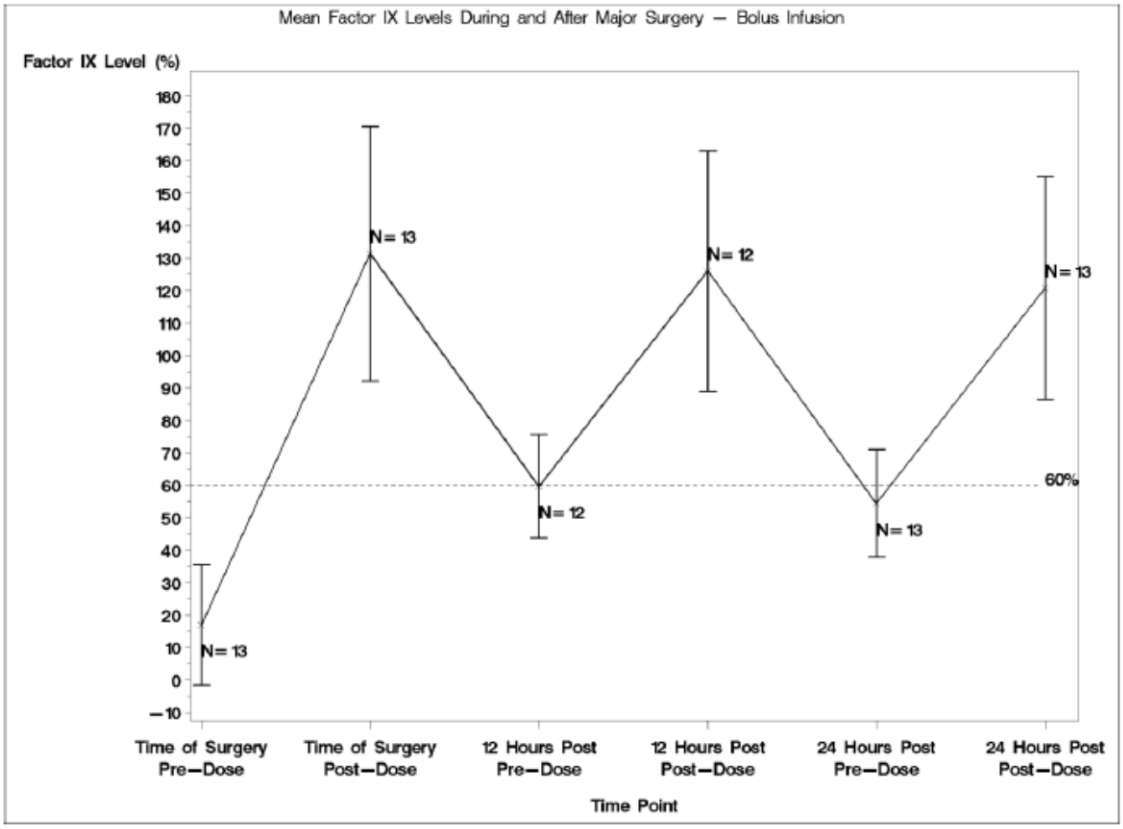
Episodic bleeding (spontaneous plus post-traumatic) occurred in 83% of subjects on-demand (n = 10 subjects), totaling 222 bleeding episodes [222 / 10 = 22 bleeding episodes per subject with bleeds]. Treatment of bleeds required 1.6 ± 1.8 infusions (median 1 infusion, range: 1–24). Bleeds resolved after one or two infusions in 33% of bleeding episodes (n = 169 bleeds) or 5% (n = 25), respectively. Only 1% (n = 4) required ≥ 5 infusions and the maximum was 20 infusions. Most of the bleeding episodes that required many infusions were related to surgery [presumably minor or not Surgery Substudy], trauma, target joints, and/or muscle bleeds. Subjects rated the efficacy of treatment for episodic bleeds as excellent, good, fair, or poor in 28%, 56%, 14%, or 2%, respectively.

Reviewer comment: The number 33% for number of infusions needed is likely an error reported in the Summary of Clinical Efficacy, and we calculate closer to 70%. A comment is included for clarification.

The largest number of bleeding episodes for an on-demand subject was an ABR of 38. After switching to prophylaxis, the ABR dropped to 4.

4. Surgery Substudy: Sixteen subjects, aged 12-56 years of age, underwent 19 major operations. Target factor IX levels were achieved by both bolus and continuous infusion regimens [Source: 125426/0.18, e0019, Synopsis, p. 16]. Twelve subjects had 13 procedures that were managed with 78 bolus infusions in aggregate. Mean dose per bolus was 60 IU/kg (median 60 IU/kg; range 24-120 IU/kg). Mean levels were kept at or above 60%, although the error bars show that some individuals must have been below 60%.

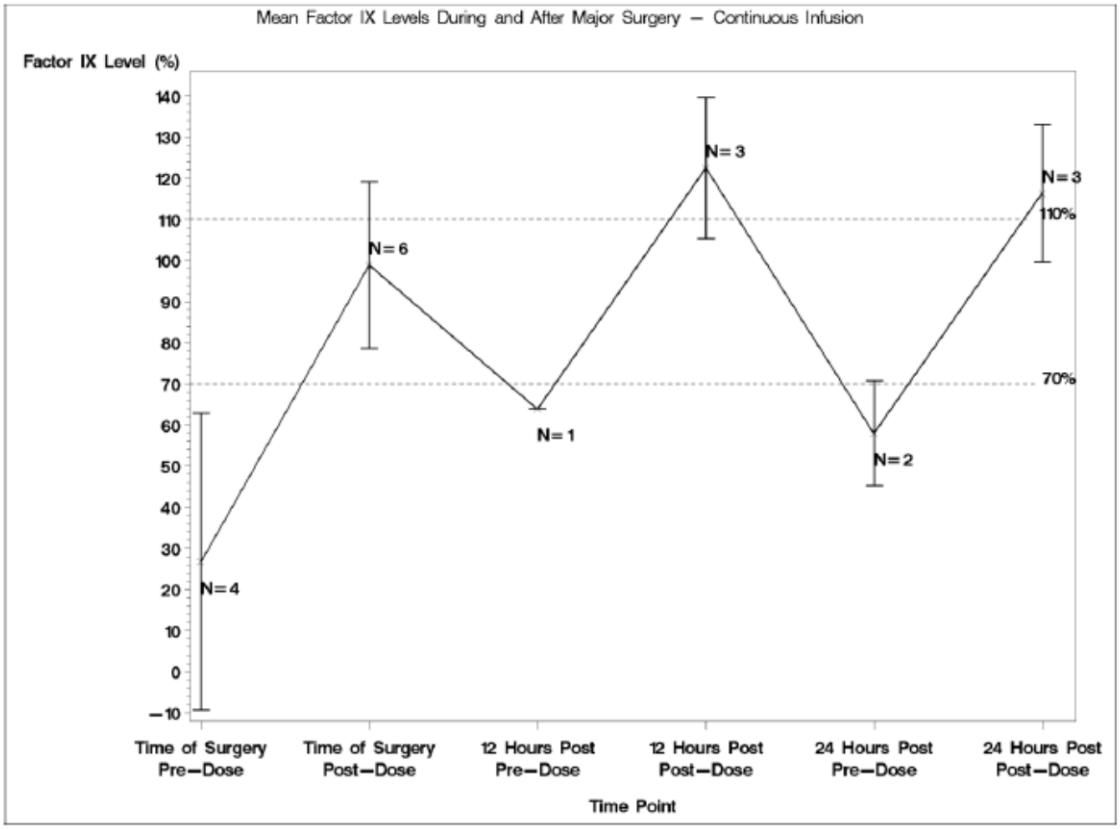
Figure. Mean Factor IX Level During and After Major Surgery - Bolus Infusion



[Source: 125426/0.18/e0019, *Report Body*, Table 11:3, p. 79]

Four subjects had six procedures that were managed with continuous infusion. Mean loading dose was 95.4 IU/kg (median 99 IU/kg; range 67-109 IU/kg) followed by mean maintenance infusion of 7 IU/kg/hr (median 7 IU/kg/hr; range 30-21 IU/kg/hr). Mean levels were kept between 49-142%:

Figure. Mean Factor IX Level During and After Major Surgery - Continuous Infusion



[Source: 125426/0.18/e0019, *Report Body*, Table 11:4, p. 81]

Effective hemostasis during and after surgery were obtained with bolus and with continuous infusion regimens. Blood loss during surgery was as expected or less than expected in 68% or 32%, respectively. Hemostasis at 12 hours and 24 hours were rated as superior or adequate at both time points in 37% and 63%, respectively. No instance of poor hemostasis was recorded. No transfusions during surgery were needed. [Source: 125426/0.18/e0019, *Report Body*, p. 87]

Table. Efficacy of IXINITY for Major Surgical Procedures

Procedure (Number)	Assessment of Response	
	Blood Loss at Surgery (Number)	**Hemostasis at 24 Hours (Number)**
Knee Arthroplasty (n = 8)	Expected (8)	Adequate (6), superior (2)
Elbow Arthroplasty (n = 2)	Expected (2)	Adequate (2)
Knee Amputation (n = 1)	Expected (1)	Superior (1)
Percutaneous Achilles Tendon Lengthening (n = 1)	Expected (1)	Adequate (1)

Open Inguinal Hernia Repair (n = 1)	Less than expected (1)	Superior (1)
Tibiotalar Fusion (n = 1)	Less than expected (1)	Adequate (1)
Arthroscopic Synovectomy (n = 2)	Expected (1), less than expected (1)	Adequate (2)
Debridement of Ankle or Knee (n = 3)	Expected (2), less than expected (1)	Superior (2), adequate (1)

[Source: Adapted from *Draft Package Insert*, Amendment 26, Table 7]

5. Mod-IB1001 Continuation Phase: All seven subjects who transitioned as of 2014-02-28 were on prophylaxis. The sample size of seven subjects is too small to draw definitive conclusions, and the duration of follow up is short. The observed bleeding rate with mod-IB1001 in the seven subjects is consistent with prior observations. The investigators judged mod-IB1001 to be effective.

   Data from infusion logs and diaries indicated that four new bleeding episodes in three subjects occurred during the mod-IB1001 Phase. One in one subject was likely a spontaneous breakthrough bleed and one bleed in another subject was post trauma. Two bleeds in one subject may have been due to compliance. The diaries were not available at the time of this report. Efficacy for prophylaxis as assessed by investigators was effective for all subjects at 5 exposure days and at months 1, 2, and 3 of mod-IB1001 treatment. Efficacy of on-demand treatment for the two episodes in two subjects with diaries was assessed as good. ABR were not calculated due to the short duration of follow up. [Source: 125426/0.23/e0024, *Supplemental Clinical Study Report*, pp. 12, 55-57]

   Reviewer comment: Page 12 of the supplemental clinical study report in e0024 mentions two ratings of bleeding episodes by subjects under prophylaxis. One is described as spontaneous, a term often used for subjects receiving an on-demand regimen, so presumably this is a spontaneous breakthrough bleed. A comment is drafted requesting clarification if this was a breakthrough bleed on prophylaxis, or a spontaneous bleed while subject was off prophylaxis.

   Reviewer comment: Section 11.4.1.2.1.1 in Amendment 125426/0.23 Sequence e0024 states that some data from bleeding diaries could not be obtained in time for the report. A comment is drafted that requests that data.

   One subject missed two bleeding episodes but also missed a number of infusions. The relationship of the bleeds to the compliance issue is speculative. Also, safety endpoints were missing in 50% of subjects (5/10). [Source: 125426/0.23/e0024, *Supplemental Clinical Study Report*, p. 49].

Rating	Deviation Code	Overall N* = 10 N (%)
Major	3. Study Visits	2 (20.0%)
Minor	4. Subject non-compliance	3 (30.0%)
	6. Safety endpoint assessments	5 (50.0%)
* Total number of protocol deviations		

[Source: 125426/0.23/e0024, *Supplemental Clinical Study Report*, p. 49]

Reviewer comment: Safety endpoints were missing in 43% of subjects (3/7 subjects). A comment is drafted requesting clarification, significance, and response.

a. PK on Mod-IB1001: Recovery parameters for orig- and mod-IB1001 were similar. This is further deferred to the PK reviewer. [Source: 125426/0.23/e0024, *Supplemental Clinical Study Report*, pp. 12, 52]

6.1.11.3 Subpopulation Analyses

- Modified Phase: Subpopulation analysis was not done in this population.
- Pediatrics: Average adjusted recovery was 0.81, 0.83, and 0.74 for subjects ≤ 18 years old, 12-18 years, <12 years, respectively, initial dosing followed by monitoring and individual dose adjustment is recommended [Source: 125428/0.18, *2.7.3 Summary of Clinical Efficacy*, p. 44]. Full PK analysis was not done for any subjects < 12 years old (actually < 14 years old) [Source: 125426/0.32, e0033, *Pediatric Deferral Request*, p. 7].

6.1.11.5 Exploratory and Post Hoc Analyses

- No product-product or disease-disease analyses were done for Treatment Phase, Continuation Phase, or mod-IB1001 Phases.

6.1.12 Safety Analyses

6.1.12.1 Methods

- The total number of subjects exposed to the test article orig-IB1001 was 77 subjects, with 9641 infusions (median 116 infusion) administered and mean exposure of 138 exposure days (ED). There were 55 subjects with ≥ 50 ED and 45 subjects with ≥ 100 ED. Safety analysis includes data from 2009-02 to 2013-03. Particular attention was paid to generally recognized important safety issues including thrombogenicity, immunogenicity, anaphylaxis, hypersensitivity, inhibitor formation, viral and prion transmission, and nephrotic syndrome.
- Total exposures in the different phases were:
  - PK Phase: Body weight ranged from 51-145 kg, so exposures in this phase ranged from 3,818-10,808 IU per subject.
  - Treatment Continuation Phases: Total exposure is 9395 days as of 2013-03-01. Mean exposure was 138 days (median 128 days). Mean

exposure for prophylaxis and on-demand groups were 149 days (median 136 days) and 84 days (median 94 days), respectively.

- o Surgery Substudy: Exposure ranged from 4-16 days, with cumulative doses up to 144,397 IU.

- Safety and exposure data reported from the mod-IB1001 Continuation Phase derive from treatment with mod-IB1001 only. Seven subjects experienced a median of 23 ED (range 10-28 ED) and underwent 146 infusions. The mean dose was 76 IU/kg, median dose 75 IU/kg, range 75-78 IU/kg. Dosing was stable. Drug was infused every 3.6 days (median: 3 days; range: 1-7 days). [Source: 125426/0.23/e0024, *Supplemental Clinical Study Report*, pp. 60-61]
- Adverse reactions are defined as adverse events that were considered related to the test article. Criteria for assessment of seriousness, severity, and causality of adverse events were provided in125426/0.23/e0024, *Supplemental Clinical Study Report*, p. 41. Adverse events were considered related if not categorized as unrelated, probably not related, or remotely possibly related.
  - o Relatedness for many types of acute events were defined as an occurrence within 24 hours of product administration.
- Definitions for immunogenicity: Negative for anti-CHOP is defined as negative at all time points, or in the instance of missing screening is negative for anti-CHOP and (b) (4) at all time points. Positive for anti-CHOP is negative at screening and thereafter for ≥ 1 time point is positive for anti-CHOP and negative for (b) (4) . All other results are indeterminate. Antibodies to factor IX are categorized similarly with an additional layer for inhibitory and noninhibitory.

6.1.12.2 Overview of Adverse Events and Reactions

Adverse Reactions - Orig-IB1001:

- For original IB1001 (orig-IB1001), adverse reactions were determined in 15 of 449 AEs (3% of events were reactions) in 7 of 77 subjects (9% of subjects had reactions). The most common, related adverse reactions were headaches with 5 events in 2 of 77 subjects (3% of subjects). Reactions were mild (n = 8, in six subjects) or moderate (n = 7, in two subjects). No severe reactions were reported.
- No anaphylactic reactions were reported in any subject. No renal reactions, such as nephrotic syndrome, were reported in the trial. Long-term safety assessment showed no differences compared with the general population. Long-term safety was defined in populations with 50 or 100 exposure days.

Table. Adverse Drug Reactions Involving IB1001 Reported in Study IB1001-01

MedDRA Standard System Organ Class	Adverse Reaction	Number of Events	Number of Subjects (n = 77) (%)	% per Infusion (n = 9641)
Congenital, familial, and genetic disorders	Hemophilia	1	1 (1.3%)	0.01%

General disorders and administration-site conditions	Asthenia	1	1 (1.3%)	0.01%
	Injection site discomfort	1	1 (1.3%)	0.01%
Infections and infestations	Influenza	1	1 (1.3%)	0.01%
Investigations	Anti factor IX antibody positive	1	1 (1.3%)	0.01%
Nervous system disorders	Headache	5	2 (2.6%)	0.05%
	Dysgeusia	1	1 (1.3%)	0.01%
	Lethargy	1	1 (1.3%)	0.01%
Psychiatric disorders	Apathy	1	1 (1.3%)	0.01%
	Depression	1	1 (1.3%)	0.01%
Skin and subcutaneous tissue disorders	Rash pruritic	1	1 (1.3%)	0.01%

The one adverse reaction of exacerbation of hemophilia in the table above was reported as possibly related but this subject was having substantial life issues and infused another product during that interval, so the relationship is not clear to this reviewer. [Source: Table adapted from 125426/0.18/e0019, *Report Body*, Table 12:6, p. 103]

The one case of pruritic rash came out of the Surgery Substudy. One case of noninhibitory anti-FIX antibody was reported as an adverse reaction.

> *Reviewer comment: The reason for selective inclusion of this one case out of many is not clear. A comment is included.*

Adverse Events - Orig-IB1001:

- Overall, 449 adverse events were reported in 58 subjects (75% of subjects) in the entire IB001-01 study. There were 14 serious events, all considered unrelated. No deaths were reported. For prophylaxis, 347 events were reported in 49 subjects. All 14 serious events occurred in the prophylaxis group.
- The most commonly reported events by preferred term in > 10% of subjects were headaches (17%, n = 37 events), arthralgia (16%), pyrexia (13%), nasopharyngitis (12%), and limb injury (10%). Headache was the most common AE reported in the prophylaxis group (17%) and on-demand group (33%). Also, if listed by SOC in > 5% of subjects, the most common listings are infections and infestations (38%), injuries (34%), musculoskeletal (32%), and neurological (31%). The overall list of adverse events is given in Table 8 in 125426/0.18/e0019, *Summary of Clinical Safety*, pp. 28-36, and further detailed in the *Displays of Adverse Events* in 125426/0.18/e0019, *Report Body*, Section 14.3.1, p. 256. For prophylaxis, the most common events were arthralgias (19% of subjects) and headaches (17%). Overall, events were mild in 68% (304 / 449,

in 54 subjects), moderate in 27% (121 / 449, in 36 subjects, or severe in 5% (23 / 449, in 11 subjects). Thrombotic events, hypersensitivity, anaphylaxis, and nephrotic syndrome were not reported.

- *Reviewer comment: Page 52 of the Summary of Clinical Safety states that nine events were probably related and seven events were possibly related to study drug, which should add up to 16 adverse reactions. However, only 15 reactions are reported. A letter-ready comment was generated.*

The frequency of adverse events per injection was < 1%.

- Surgery SubStudy: The study is too small to make statistically meaningful observations, although no obvious safety signal was noted. Ten of 17 subjects experienced 33 adverse events. No AE was serious. AE were mild in 25 events, 7 were moderate, and 1 case of end-stage arthritis was included. One subject required a transfusion in the postoperative period, which was considered expected given the difficulty and extent of the operation. Pyrexia was the most common event, seen in 18% of subjects.
- For mod-IB1001 administered to seven subjects:
  - No subjects developed inhibitory FIX antibodies. One subject had a positive test for noninhibitory FIX antibodies followed by several negative tests.
  - No significant change in anti-CHOP antibody status occurred. Five subjects were negative for anti-CHOP prior to administration of mod-IB1001 and they all stayed negative. One subject who became positive for anti-CHOP during original IB1001-01 maintained stable levels of anti-CHOP. One subject who was positive for anti-CHOP at the beginning of original IB1001-01 and then considered indeterminate prior to administration of mod-IB1001 remained indeterminate because of consistent non-specific binding.
  - The clinical and laboratory safety profiles are consistent with original IB1001. A total of 14 AE were observed. Ten events in four subjects were mild and four events in two subjects were moderate. No AE was severe. There were no serious adverse events. None of the events were considered related to the product, thus none were adverse reactions. There were no allergic reactions or decrease in efficacy. [Source: 125426/0.23/e0024, *Supplemental Clinical Study Report*, pp. 62-64]

Table. Summary of Adverse Events by Preferred Term, mod-IB1001

Preferred Term	Events	Subjects, n (%)
Abdominal pain	1	1 (14%)
Peripheral edema	1	1 (14%)
Diverticulitis	1	1 (14%)
Fungal skin infection	1	1 (14%)
Gastroenteritis viral	1	1 (14%)
Influenza	1	1 (14%)
Nasopharyngitis	1	1 (14%)

Limb injury	1	1 (14%)
Back pain	2	2 (29%)
Migraine	1	1 (14%)
Nephrolithiasis	1	1 (14%)
Rhinorrhea	1	1 (14%)
Acne	1	1 (14%)

[Source: Adapted from 125426/0.23/e0024, *Supplemental Clinical Study Report*, pp. 63-64]

The moderate events were diverticulits, migraine, limb injury, and nephrolithiasis.

- Long-term safety assessment showed no differences compared with the general population. Long-term safety was defined in populations with 50 or 100 exposure days.

6.1.12.3 Deaths

- No deaths were reported in any aspect of the trial.

6.1.12.4 Nonfatal Serious Adverse Events

- No related serious adverse reactions were reported. There were 14 serious adverse events, all considered unrelated. All required hospitalization and came from the Treatment/Continuation Phase. The most frequent unrelated SAE were infections, or injuries, including diverticulitis or wound infections. Less frequent were vascular (hematoma), abdominal pain, or psychiatric. One SAE of a wound infection was considered life threatening, and others were severe, moderate or mild in seven, five, and one, respectively.

6.1.12.5 Adverse Events of Special Interest (AESI)

- **Immunogenicity:** Two types of immunogenicity of special interest were development of antibodies against Chinese hamster ovary host cell proteins (anti-CHOP) and against factor IX (anti-FIX).
  - *Anti-CHOP Antibodies (Anti-CHOP):*
    - For original IB1001 at the time of clinical hold, anti-CHOP were demonstrated in 18 of 68 subjects (26%) in Treatment/Continuation Phase developed anti-CHOP. No clinical effect of the anti-CHOP antibodies was identified on efficacy or adverse event profile while on orig-IB1001. No excess allergic reactions, rashes, anaphylaxes, renal diseases, or arthropathies were identified. Subjects who elected to remain on study were followed with enhanced monitoring, including immunogenicity testing every 3 months. An additional two subjects converted, for a final total of 20 out of 68 subjects (29%) with anti-CHOP at data lock.

      In Treatment/Continuation Phase in which there was 406 events reported, 224 of the events were in anti-CHOP negative subjects.
    - Simultaneous with the additional (b) (4) step was added to manufacturing to remove host cell proteins, the HCPs were characterized and

and assay to monitor the HCPs was validated. Nonclinical comparability studies showed that mod-IB1001 was comparable to orig-IB1001 in physiochemical and biological characteristics.

- In the updated immunogenicity report in Sequence e0019, data was collected out to 2013-10-15.
  - Two additional subjects seroconverted to positive for anti-CHOP. Thus, the anti-CHOP incidence had increased to 20 of 68 subjects (29%) of subjects in IB1001-01. Conversely, 37 subjects (54%) remained negative for anti-CHOP [Source: 125426/0.18/e0019, *Immunogenicity Risk Assessment*, p. 4]. A group of 11 subjects (16%) were collated who were baseline positive, or had sporadic or indeterminate anti-CHOP results. No safety concerns have been identified in the subjects' adverse event profiles related to the anti-CHOP antibodies. Subjects have been followed after seroconversion for a median of 414 days [Source: 125426/0.18/e0019, *Summary of Clinical Safety*, p.85].
  - In eight of nine subjects, anti-CHOP titers have decreased. [Source: 125426/0.18/e0019, *Immunogenicity Risk Assessment*, p. 9]
  - Mod-IB1001: Seven subjects who transitioned to mod-IB1001 by 2014-02-28 were stable after transition, and did not increase or develop anti-CHOP titers. Five subjects that were negative remained negative. Two subjects were positive after orig-IB1001; one was stable after transition, and one went from positive while on orig-IB1001 to indeterminate before and after transition.

o *Anti-FIX Antibodies:* No FIX inhibitors (neutralizing antibodies) have been identified in any subject. Transient noninhibitory anti-FIX antibodies were found in 27% of subjects (21 / 77), 16 of whom who were negative at baseline [Source: 125426/0.18/e0019, *Immunogenicity Risk Assessment*, p. 18]. No safety concerns have been identified in the subjects' adverse event profiles related to the transient, noninhibitory anti-FIX antibodies. Treatment doses remained stable.

- One case of noninhibitory anti-FIX antibody was reported as an adverse reaction. It is not clear why this one case was selected as related.
- Mod-IB1001: None of the seven subjects who transitioned to mod-IB1001 by 2014-02-28 developed inhibitors. One subject developed a transient, single positive test for non-inhibitory, followed by several negative results.

- **Thrombogenicity:** Thrombogenicity was an AESI and assessed as a secondary safety endpoint during the PK Phase. Increased thrombogenicity was defined as simultaneous positivity of three markers: TAT, D-dimer, and PTF1+2. No subject had all three endpoints positive simultaneously and there were no clinical thromboembolic events [Source: 125426/0.18/e0019, *Report Body*, p. 106].

- **Mod-IB1001 Phase:**
  o As of 2014-05-12, updated data was available for the seven subjects initially described in *Supplemental Clinical Study Report* from 125426/0.23, e0024, five additional subjects transitioned since 2014-02-28, and five subjects who remain eligible for transition pending regulatory approval. [Source: 125426/0.26, e0027 *Response*, p. 1]

- Subject (b) (6) (from group of first seven transitioned) had anti-CHOP titers of 349 prior to transition and after transition had titers of 440, 427, and 314 at times 5 exposure days, 1 month, and 2 months respectively. [p. 1]
- Subjects (b) (6) transitioned in 2014-03 and have completed Visit ED5. Subjects (b) (6) were negative for anti-CHOP at baseline and Visit ED5. Subject (b) (6) had anti-CHOP titer of 338 before transition. Subsequent measurements are pending.

Subject; (Transition Date)	Mod-IB1001 Baseline	ED 5	1 Month	2 Months	3 Months	6 Months Scheduled	Monitoring of Most Recent Visit Scheduled, Labs Expected
(b) (6)	neg[b]				CSR[a]	2014-4/5[a]	2014-5/6[a]
	neg[b]				CSR[a]	2014-4/5[a]	2014-5/6[a]
	neg[b]				CSR	2014-4/5[a]	2014-5/6[a]
	neg[b]				CSR	2014-4/5[a]	2014-5/6[a]
	indet				CSR	2014-4/5[a]	2014-5/6[a]
	neg[b]				CSR	2014-4/5[a]	2014-5/6[a]
	349[a]	440[a]	427[a], ED 11	314[a]	2014-04[a]		2014-05
(2014-03)	neg[a]	neg[a]					
(b) (6); (2014-03)	338[a]	pending[a]					2014-05[a]
(b) (6) (2014-03)	neg[a]	neg[a]					
(b) (6) (2014-04-15)	pending[a]						2014-05[a]
(b) (6) 2014-04-15)	pending[a]						2014-05[a]

[a] [Source: 125426/0.26, e0027 *Response*]

[b] [Source: 125426/0.23, e0024, *Supplemental Clinical Study Report*]

6.1.12.6 Clinical Test Results

- Orig-IB1001: Analysis of laboratory values for orig-IB1001 did not demonstrate any safety signals.

Mod-IB1001: Laboratory analysis of the seven subjects transitioned by 2014-02-28 did not demonstrate any safety signals. [Source: 125426/0.23/e0024, *Supplemental Clinical Study Report*, p. 11]

6.1.12.7 Dropouts and/or Discontinuations

- As of 2013-03-01, 43 subjects in the Treatment or Continuation Phases had discontinued the study. Some subjects were withdrawn by the investigators due to anti-CHOP antibodies and others withdrew following the clinical hold. A few had enrolled for a limited time and some moved. Five were terminated for lack of compliance. No subjects withdrew due to adverse events. One withdrew due to a perceived lack of efficacy, although there were conflict life issues that may have played a substantial role. [Source: 125426/0.18/e0019, *Report Body*, pp. 58-59]

6.1.13 Study Summary and Conclusions

Efficacy Conclusions:

- The BeneFIX/orig-IB1001 PK study showed no significant differences in AUC or C(max). The repeat PK study at 6 months was comparable.
- The ITT population for the Treatment Population were aged 7 - 64 years and most had experienced bleeds in ≥ 2 large joints. Most of the ITT population were treated on prophylaxis. A small fraction was treated on demand.
- For prophylaxis, the annualized bleeding rate for subjects was 1.33 ± 1.35 (95% CI = 0.99 - 1.68). Treatment regimens were usually rated by investigators as effective with a few partially effective. No treatments were rated as "not effective." For treatment of breakthrough bleeding, IB1001 was rated as effective in terms of (1) time of bleed, (2) time for resolution of pain associated with bleed, or (3) time for resolution of swelling. Subjects rated efficacy for treatment of bleeding as excellent in 51% and good in 32% of episodes. Treatment required a mean of 1.9 ± 2.2 infusions per episode.
- For on-demand subjects, the annualized bleeding rate was 3.55 ± 1.97 (95% CI = 2.29 - 4.80). All except one treatments were rated by investigators as effective, with the single other case rated partially effective. Subjects rated efficacy for treatment as excellent in 28% and good in 56% of episodes. Treatment required a mean of 1.6 ± 1.8 infusions per episode.
- For surgery, both bolus and continuous-infusion regimens were effective for hemostasis during and after surgery. Blood loss was as expected or less than expected in all procedures. No transfusions were required during surgery, although one subject required transfusion in the postoperative period because of persistent bleeding.
- IB1001 is effective for its claimed indications.

Safety Conclusions:

Original IB1001 (orig-IB1001):

- For orig-IB1001, the most important safety issue was development of immunogenicity to CHO host cell proteins in at least 20 of 68 subjects (29%) in the Treatment Phase, which resulted in the program for orig-IB1001 being placed on clinical hold. No adverse reactions have been observed in these subjects. That product will no longer be used and will not be marketed. The CHO host cell protein issue will not be extrapolated to mod-IB1001 and the immunogenicity of mod-IB1001 will be evaluated on its own.
- Aside from the immunogenicity issues, comparability studies have shown the active ingredient to be comparable, and the remainder of the non-immunogenic adverse event profile of orig-IB1001 will be extrapolated to mod-IB1001. There were no deaths or related serious adverse reactions identified. Related adverse reactions to orig-IB1001 were identified in 7 of 77 subjects (9%), with 15 adverse reactions all being mild or moderate in severity. The most common reactions were headaches with 5 events in 2 subjects (3% of subjects). No subject tested positive to thrombogenic markers in the PK phase and no thrombotic events were reported. The safety profile at 50 and 100 exposure days is similar to the general safety profile.
- No inhibitory antibodies to factor IX were developed. Binding, noninhibitory, non-neutralizing antibodies were found in 21 subjects [27%]. Dosing remained stable and no adverse reactions were related.

Modified IB1001 (mod-IB1001):

- The number of subjects with safety assessment for mod-IB1001 is too small to determine the safety of mod-IB1001. Data from seven subjects has been submitted, but the letter lifting clinical hold recommended 20 subjects.
- No inhibitors to factor IX or increases in anti-CHO antibodies have been identified. No safety signals have been identified.

- Overall, the safety profile in the absence of CHO host cell proteins is considered acceptable and expected, and the safety-risk ratio is favorable.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

- Not studied.

9.1.2 Use During Lactation

- Not studied.

9.1.3 Pediatric Use and PREA Considerations

- Timelines:
    - 2010-09: Inspiration filed 13551, e0029, which contained a pediatric plan.
    - 2010-10-14: Pediatric plan was discussed during end-of-phase, type B meeting.

- 2012-05-14: Pediatric plan submitted with 125426/0.3, e0003.
- 2013-07: FDA publishes draft guidance on pediatric study plans.
- 2013: Under 13551, e0079, FDA agrees that submission of an iPSP is not required.
- 2014-06-18: Presentation before the PeRC. The PeRC said that the provided inromation was acceptable.

- Partial waiver: Pediatric partial waiver for infants 0 - 27 days was requested for both indications (treatment, surgery). The applicant claimed that inclusion of this age group was impractical because number of patients is so small. Incidence of hemophilia B is 1 in 50,000 people. [125426/0.3 Pediatric Waiver Request]
  - On 2014-06-16, the request for partial waiver for 0 - 27 days was denied.
- Deferral: Pediatric deferral for infants and toddlers 1 to < 24 months and children 2 to < 12 years was requested because partial deferral for infants, toddlers, and children 1 month to < 12 years is standard practice for coagulation factors, where studies are sequenced through previously treated adults and adolescents, then previously treated pediatric children younger than adolescent, then previously untreated children. Because the waiver of 0-27 days was denied, the deferral was expanded to 0 months - 12 years.
- Study IB1001-01: Included subjects ≥ 12-15 years old with PK, safety, and efficacy asessments. Pediatric assessment for IB1001-01 is as follows:
  - Six subjects ages 12 to < 16 years have been enrolled, two 12 years and four 14 years. Nine adolescents aged 12 to < 18 years have been studied [Clinical Overview, p.68]. Three subjects were < 12 years old [Source: 125426/0.18/e0019, *Summary of Clinical Safety*, p. 21].
  - Pediatric subjects aged 12 to < 18 years showed an average adjusted recovery lower than in adults. Dose adjustment is recommended.
  - On 2014-06-18, the submission was presented to PeRC. The PeRC accepted our assessment of the pediatric part of the submission, and agreed with the request for deferral of subjects <12 years old.
- Study IB1001-02: Study IB1001-02 will study previously treated children ≤ 12 years. The study is planned for ≤ 22 subjects to accrue 10 each in age groups < 6 years and 6 to ≤ 12 years.
  - *Reviewer note: IB1001-02 Protocol Amendment 5 specifies ≤ 12 years in the synopsis and body of protocol, not < 12 years as in Deferral Request in e0033, p. 3*

  The study will assess PK followed by treatment for ≥ 50 exposure days in 20 subjects. The surgical indication is not mentioned. Subjects initially were to come from the U.S., U.K., and India. Enrollment into IB1001-02 has been difficult in countries where other products are available since parents do not wish to subject their progeny to PK studies with multiple blood draws. In India, where most of the subjects have been enrolled, the children have been able to access care otherwise unavailable.
- Study IB1001-03: Previously contemplated Study IB1001-03 has been discontinued before initiation. The EMA no longer suggests these protocols for

products that are not novel. [Sources: 125426/0.32, cover letter; European Medicines Agency (EMA) Guideline on the Clinical Investigation of Recombinant and Human Plasma-Derived Factor IX Products (EMEA/CHMP/BPWP/144552/2009, 21 July 2011]

- Study IB1001-04: Study has been approved under IND 13551 in U.S. Study is on internal company hold pending determination of a strategy for Europe. [Sources: 125426/0.32, cover letter]

- Pediatric Timelines and Other Pediatric Data are provided in the table below.

Study	IB1001-01	IB1001-02	IB1001-04
Age Range	Current indication claim and ongoing Continuation Phase ≥ 12 yrs	< 12 years	≥ 12 yrs
Population	Previously treated, severe hemophilia B with activity ≤ 2 IU/dL	Previously treated, severe hemophilia B with activity ≤ 2 IU/dL	Previously treated, severe hemophilia B with activity ≤ 2 IU/dL, naïve to IB1001
Number of Subjects	≥ 50 evaluable on prophylaxis, ≥ 18 on demand, ≥ 10 surgery, ≥ 28 for PK.	20 subjects, half < 6 yrs and half 6-12 yrs. As of Amendment #5, no new subjects will be enrolled.	12 subjects
Protocol Design	PK, safety, efficacy, surgery, immunogenicity. PK was randomized, crossover. Safety, efficacy, and surgery were open label, uncontrolled.	Safety, efficacy. Design similar to IB1001-01. Accommodations for pediatric subjects include reduced time points and blood collection and increased monitoring during the first 25 ED.	Safety, PK, efficacy, thrombogenicity, immunogenicity. Single-arm, open-label design with PK, treatment, and continuation phases.
Duration	12 months in ongoing Continuation Phase, 6 months for completed Treatment Phase	50 exposure days	50 exposure days
Location	23 sites in 7 countries including U.S.	UK, India	Still under development
Completion of Clinical Trial (projected)	Treatment Phase is complete. Continuation Phase: 2015-July	2017-Q2 or 2017-Q3	Unknown
Submission of Final Study Report (projected)	Treatment Phase is submitted to BLA. Continuation Phase: 2016-Q1	2017-Q4	Unknown

9.1.4 Immunocompromised Patients

- The population are all immunocompromised as an inclusion criterion. Certain types of immunocompromise are exclusion criteria. Subpopulation analysis not applied to the different types of humoral immunodeficiency.

9.1.5 Geriatric Use

- Subpopulation analysis not done.

10. CONCLUSIONS

- The manufacturing process for modified rFIX now includes an extra (b) (4) to remove contaminants. IB1001 was found to be effective in treatment and perioperative populations.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.2 Risk-Benefit Summary and Assessment

- At the time a regulatory action of CR was chosen for product and manufacturing issues, the clinical benefit-risk ratio was favorable. The current product has been shown to be comparable to product before modification, so efficacy was extrapolated from orig-IB1001. The efficacy profile was acceptable. The main safety issue was the anti-CHOP antibodies that led to clinical hold. These had no clinical ramifications, and the rest of the safety profile was acceptable. The host cell proteins have been substantially reduced with a modification in the manufacturing process. No factor IX inhibitors were found, although non-inhibitory antibodies were found in over 20%, again with no clinical consequences. Thus, the anticipated safety profile of the current product is expected to be acceptable. Complete data is available on seven subjects with mod-IB1001. It is anticipated that more data on the current product will be available upon submission.

11.4 Recommendations on Regulatory Actions

- Decision has been made to provide complete review letter because of inspectional and product issues. Clinical recommendation is to include open clinical and statistical questions to the applicant as part of the CR letter.

11.5 Labeling Review and Recommendations

- 2014-05-09: FDA sends information request to update prescribing information with data from mod-IB1001 and to remove indications for secondary, tertiary, and intermittent prophylaxis.
- 2014-05-12: Teleconference which concludes with understanding that Rixubis has orphan exclusivity for factor IX prophylaxis indications and that prophylaxis claims should be removed from IXINITY label.

- 2014-05-14: Revised label submitted in e0027. This included data from subjects transitioned to mod-IB1001, improvements in Section Instructions for Use, and transfer to Emergent BioSolutions
- Labeling review halted once CR letter became regulatory action. Full labeling review will begin upon resubmission.

11.6 Recommendations on Postmarketing Actions

- None at present time. Will be reconsidered upon resubmission.

Appendix A: Documents Reviewed and Timelines

- Amendments to 125426/0 after the initial resubmission of 125426/0.18, e0019 are listed here.
    - 2014-01-27, e0019, Amendment 0.18
    - 2014-03-05, e0020, Amendment 0.19
    - 2014-03-06, e0021, Amendment 0.20
    - 2014-03-21, e0022, Amendment 0.21
    - 2014-04-14, e0023, Amendment 0.22
    - 2014-04-22, e0024, Amendment 0.23, Supplemental Clinical Study Report.
    - 2014-04-30, e0025, Amendment 0.24, Response to CMC IR of 2014-04-21.
    - 2014-05-05, e0026, Amendment 0.25, Responses to two CMC IRs of 2014-04-21.
    - 2014-05-12, e0027, Amendment 0.26, Revised labeling
    - 2014-05-20, e0028, Amendment 0.27, Response to IR of 2014-04-28
    - 2014-05-29, e0029, Amendment 0.28, Response to statistical IR of 2014-05-22
    - 2014-06-03, e0030, Amendment 0.29, Closure CMC
    - 2014-06-05, e0031, Amendment 0.30, CMC, (b) (4)
    - 2014-06-10, e0032, Amendment 0.31, CMC, lot samples
    - 2014-06-17, e0033, Amendment 0.32, Pediatric deferral request and timeline
    - 2014-06-17, e0034, Amendment 0.33, CMC information in response to the 483 observations generated during inspection
    - 2014-06-30, e0035, Amendment 0.34, (b) (4) and Closure CMC
    - 2014-07-07, e0036, Amendment 0.35, CMC responses
- Information from IND 13551 was examined.
    - Amendment 13551.72, Serial e0072: Clinical hold complete response
    - Amendment 13551.73, Serial e0073: Type A meeting request
    - Amendment 13551.74, Serial e0074: Withdrawal of Type A request
    - Amendment 13551.75, Serial e0076: Updated investigators
    - Amendment 13551.76, Serial e0077: Revised general investigation plan, protocols
    - Amendment 13551.77, Serial e0078: Annual report until 2013-08-28
    - Amendment 13551.78, Serial e0079: About Pediatric Study Plan

- Amendment 13551.79, Serial e0080: New investigators
- Amendment 13551.80, Serial e0081: Revised protocol
- Amendment 13551.81, Serial e0082: Doing business under Emergent

TIMELINE:

An updated consolidated report was submitted with report date of 2014-01-17. After the initial complete review letter was sent on 2013-02-01, Inspiration Biopharmaceuticals declared bankruptcy and the rights to the product were acquired by Cangene Corporation. Cangene Corporation is now doing business under Emergent Biosolutions. The company has reanalyzed the data out to a later date, 2013-03-01.

- 2012-05: An unanticipated number of subjects were found to have developed antibodies against CHO proteins.
- 2012-07-05: After identification of immunogenicity safety signals in 2012-05, the study was placed on clinical hold by FDA. In other countries, subjects with high anti-CHOP titers were removed from treatment with orig-IB1001 and transferred to a marketed product, while lower-titer subjects were allowed to continue with monitoring.
- 2013-02-01: A complete review letter is issued. The clinical, toxicological, and statistical issues in the letter from were:
  17. Please submit the data on recipient antibodies against factor IX in a SAS transport file (.xpt).
  18. Please modify the ACHOBAT file including revision of the patient identification field and presentation of titer values in a proper numerical and tabular format.
  19. You have not provided adequate nonclinical data to fully evaluate the safety of IB 1001 […]. Before the BLA for IB 1001 can be approved, please conduct and submit the results from the nonclinical in vivo immunogenicity studies detailed in the letter sent to you on November 29, 2012.
  21. We are not able to replicate your results for the annualized bleeding rate in Table 11.4-7. […] Please submit your clarification to the Agency as soon as you obtain relevant information to resolve it.
  22. It is not appropriate to use the cutoff date to calculate the annualized bleed rates because the bleeding events that occurred between the last visit and the cutoff date cannot be captured in the calculation for some subjects. Therefore, the annualized bleed rate can be underestimated. […] We recommend that the annualized bleed rate should be calculated based upon the longest study period with bleeding information available. For example, the last visit date of Sept 16, 2011 should be used instead for Subject 71-002. Please submit the updated analysis.
- 2013-02-15: Inspiration declares bankruptcy.
- 2013-06-27: The applicant submitted a complete response to clinical hold letter in 13551.72. This included a general investigational plan. This general investigational plan was subsequently revised in Amendment 76, Serial e0077. The submission included physiochemical comparability data and a rat PK study. The comparability data and rat PK study did not show any significant differences between modified and original IB1001 products.
  - This original general investigational plan [subsequently changed] mentioned four studies:

    - IB1001-01 extension study continued using modified IB1001. Data before and after modification are to be combined.
    - IB1001-02 pediatric PTP study continued using modified IB1001. Data before and after modification are to be combined.
    - IB1001-03 is a planned study of modified IB1001 in pediatric PUPs < 6 years old. The protocol has not yet been submitted. This study is to follow IB1001-02 after sufficient data are available. The proposal in the letter is for 10 subjects, including 5 subjects < 6 years old, with ≥ 50 exposure days. Note that only IB1001-02 will have subjects < 6 years old. IB1001-04 is for subjects ≥ 12 years old.
    - IB1001-04 is a planned study of subjects ≥ 12 years old in support of IB1003. The letter proposes that IB1001-04 will study PK, safety, and efficacy of modified IB1001 and is not intended as to compare original and modified IB1001. The letter stated that "A Pediatric Investigational Plan will be filed prior to the CRL response package."
- 2013-07-19: Medical officer review memo stated that at the time of 13551.72, no inhibitors or clinical adverse events had been reported. Pediatric subjects < 12 years old could not be examined into IB1001-02 until the PK study had been done. It also stated that "a new clinical trial is planned to demonstrate that the reduction in HCP in the modified IB1001 does correlate with a reduced risk of immunogenicity." This memo is not in the EDR.
- 2013-07-26: In 13551.72, FDA issues the letter that lifted the clinical hold. The letter included the advice comment "You are not required to conduct an efficacy study to support licensure of your modified process. A single-dose adult safety and PK study of at least 20 naïve subjects may be adequate to demonstrate comparability to the pre-modified process product. Please submit a protocol to the IND for our review. The results of this safety and PK study can be submitted to support licensure of the product. The efficacy study can be conducted post-marketing. Please be aware that if major differences are identified in the PK comparability study, an efficacy study will be needed to support licensure." An initial pediatric study plan was also requested. Clinical Pharmacology memo has no action indicated, including to the PK proposal of recovery study. Toxicology memo has three comments. Comment (2) which stated that the rat comparability did not meet the FDA for PK comparability but would likely not increase patient risk. Comment (3) noted that the results of the rabbit comparative immunogenicity study were not available. CMC memo found no unresolved issues and recommend lifting the clinical hold.
- 2013-09-11: In 13551.73, the applicant requested a Type A meeting to clarify the advice comments in the letter of 2013-07-26. Clinical Pharmacology and Statistics recommended no action indicated.
- 2013-09-12: FDA held a teleconference with the applicant. Cover letter of e0024, dated 2014-04-22, states that applicant committed to provide additional information on mod-IB1001.
- 2013-09-13: Applicant submitted the minutes [link here] of 2013-09-12 meeting. It stated a number of things:
    - IB1001-01 will continue and modified IB1001 will be introduced into that study.
    - IB1001-02 is a pediatric study and will use modified IB1001.
    - IB1001-03 is not mentioned and I am unaware of this study.

    - IB1001-04 is a study of adult safety and efficacy which was initially proposed in the general investigation plan submitted in 13551.72. At some point this was misinterpreted as a prelicensure study [I am not sure where at this point] but was clarified to be performed postmarketing. IB1001-04 is intended as a postmarketing study to generate data prior to conducting a study in pediatric previously untreated patients (pediatric PUP, pPUP). This study is to be initiated prelicensure.
    - The PK study was interpreted [incorrectly, see 2013-09-16 below] as a postmarketing study.
    - Plan is to withdraw the request for Type A meeting, clarify the general investigational plan, and identify the clinical data that will be available for inclusion to the complete review letter. This will include a question to FDA as to whether this is acceptable.
- 2013-09-16: FDA responded to applicant by email. The response states that "The Pk study was offered in lieu of the efficacy and safety study (which we thought is your proposal to support licensure) and was intended to be completed prelicensure." Since no other comments were made on the meeting minutes, it is presumed that FDA agreed to the points.
- 2013-09-20: In Amendment 13551.74, Applicant withdrew the Type A meeting request. They stated that they would file an amendment with a general investigational plan. The amendment would ask if that might support licensure and FDA would respond with answer. Clinical Pharmacology and Statistics recommended no action indicated.
- 2013-10-18: Amendment 13551.75, Serial 76 updated investigators. There are no memos in response.
- 2013-10-30: In Amendment 13551.76, Serial 77, the revised general investigational plan was submitted. In the cover letter, the applicant planned to submit to the BLA the comparability and rat PK data from Serial 72 along with an additional rabbit immunogenicity study. The cover letter stated that preliminary data from the rabbit immunogenicity study suggests decrease in immunogenicity as shown by decreased anti-CHOP antibodies and incidence [adverse reactions?] rate. The applicant contends that the efficacy data from the original product can be extrapolated to the modified product for licensure purposes. At the time of this letter, 48 adult subjects with > 100 exposure days had been submitted to the BLA. Note that the original plan for Treatment Phase was 6 months and projected 50 exposure days, while the plan for Continuation Phase was projected > 100 exposure days. The revised plan includes the following information:
    - IB1001-04 will be initiated prelicensure but will completed postmarketing. The protocol for IB1001-04 was included in Sequence e0077 along with a revised investigator brochure. No modifications to protocol IB1001-01 were submitted.
    - IB1001-01 and IB1001-02 are reopened and can receive modified IB1001. Recovery data, including Cmax, will be collected. PK data from original and modified IB1001 can be compared using descriptive statistics. Safety and efficacy data will be also be available and the applicant plans to submit an interim report by 2014-04-15. This may also include data from IB1001-04.
    - CMC memo had information request for viral clearance information. Clinical Pharmacology and Statistics recommended no action indicated.
    - The company posed three questions:

    - Licensure based on CMC comparability, rat PK, and rabbit immunogenicity
    - PK clinical data not needed for licensure
    - Timeline for data submission from mod-IB1001
- 2013-11-06: Amendment 13551.77, Sequence e0078, Clinical Pharmacology and Statistics recommended no action indicated.
- 2013-11-22: Amendment 13551.78, Sequence e0079 contained discussion of pediatric study plan.
- 2013-12-03: Email from FDA in response to questions in Amendment 13551.76, answering yes to all three questions.
- 2014-01-28: Amendment 13551.80, Sequence e0081, Clinical Pharmacology recommended no action indicated.
- 2014-02: Cangene is acquired by, and begins to do business under, Emergent BioSolutions.
- 2014-03-07: Amendment 13551.81, Sequence e0082, no review memos.
- 2014-04-21: FDA sent two information requests, all CMC, at 11:32 AM and 5:18 PM, from Dr. Kimchi-Sarfaty, each with three items.
- 2014-04-22: Amendment 125426/0.23, e0024, is submitted. It contained a cover letter and a supplemental clinical study report. The report contains data for modified IB1001 from seven subjects in IB1001-01.
- 2014-04-28: Information request issued by DMPQ.
- 2014-04-30: Amendment 125426/0.24, e0025, is received. Is all CMC information.
- 2014-05-05: Amendment 125426/0.25, e0026, is received. Is all CMC information.
- 2014-05-09: FDA sent information request for more current data for mod-IB1001, prescribing information including revised data, and removal of indications for secondary, tertiary, and intermittent prophylaxis.
- 2014-05-12: Teleconference with Emergent which covered the prophylaxis labeling issue. Emergent reminded us that Rixubis has orphan exclusivity for factor IX prophylaxis. The conclusion was that Ixinity must remove all prophylaxis claims unless they can claim superiority, which is not the case at present.
- 2014-05-13: Amendment 125426/0.26, e0027 is submitted.
    - In response to the request for updated data on subjects treated with mod-IB1001, updated data could not be generated because of timing issues.
- 2014-05-22: Information request sent to applicant regarding two statistical issues.
- 2014-05-29: Amendment 125426/0.28, e0029 is received. Contains response to statistical IR of 2014-05-22. Applicant declines to update study report by removing the square-root transformations. Also provides data for infusions that requires clarification. They clarify that FDA agreed to allow mention of prophylaxis will be allowed in appropriate sections including clinical studies. Prophylaxis indication was removed as per teleconference of 2014-05-12. Letter-ready comments drafted.
- 2014-06-03: Amendment 125426/0.29, e0030 is received. Contains CMC information about (b) (4) test and prefilled syringes. No clinical information.
- 2014-06-04: Teleconference to discuss pediatric data. FDA requests timelines for pediatric studies. FDA is informed that Study IB1001-04 is on internal company hold.

- 2014-06-05: Amendment 125426/0.30, e0031 is received. This is CMC information about (b) (4) . No clinical information.
- 2014-06-10: Amendment 125426/0.31, e0032 is received. This is CMC information about lot sample provision. No clinical information.
- 2014-06-06: FDA conducts inspection of (b) (4) . between (b) (4) . Many deficiencies are discovered, which result in issuance of a Form 483.
- 2014-06-16: Sent email notification that the request for the partial waiver for subjects between 0 - 27 days of age was denied. The email also requested updates to pediatric studies and timelines for those studies.
- 2014-06-17: Amendment 125426/0.32, e0033, is received. This includes the response to request from 2014-06-16.
- 2014-06-17: Amendment 125426/0.33, e0034 is received. This is CMC information in response to the 483 observations generated during the inspection of (b) (4)
- 2014-06-18: Presentation before the PeRC. The PeRC said that the provided inromation was acceptable.
- 2014-06-30: Amendment 125426/0.34, e0035, is received. Information Amendment #1 continues the response in e0026 about qualifying a (b) (4) assay. Information Amendment #2 continues the responses in e0009, e0019, e0028, and e0030 about validating the (b) (4) test of sterilized syringes. Section 3.2.P.2.5, val_ev_0178_rep_v1 includes information about the (b) (4) assays and (b) (4) for factor IX potency. All documents reviewed, most were CMC.
- 2014-06-30: Compliance check finds no issues, OCBQ has no objections.
- 2014-06-30: FDA inspector reviewed Emergent's 483 response. He reviewed his Comments 7, 12, 13, 14, and 15. All of the firm's responses were adequate.
- 2014-07-07: Amendment 125426/0.35, e0036, is received.

Postmarketing Timelines

- IB1001-01, 50 ED, including mod-IB1001: Final study report - 2016-Q1
- IB1001-01, 100 ED, including mod-IB1001: Final study report - 2016-Q1
- IB1001-02: Initiation - 2011-05
- IB1001-02: Completion - 2017-Q3
- IB1001-02: Final study report - 2017-Q4
- IB1001-03: Plan discontinued

Appendix B. References

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