Application Type	Original Application
STN	125426/0
CBER Received Date	April 6, 2012
PDUFA Goal Date	April 29, 2015
Division / Office	DHCR/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)
(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

TABLE OF CONTENTS

GLOSSARY AND ABBREVIATIONS

AE(s)	Adverse Event(s)
Anti_CHOP	Anti-CHOP Antibodies
Anti-FIX	Anti-Factor IX Antibodies
AR(s)	Adverse Reaction(s)
CHO	Chinese Hamster Ovary
CHOP	CHO Protein
CMC	Chemistry, Manufacturing, and Controls
ED(s)	Exposure Day(s)
FIX	Factor IX
HCP	Host Cell Proteins
IB1001	IXINITY; Recombinant Factor IX; the test article
IB1001-01	The name of the pivotal trial, including phases 1/2/3
IB1001-02	The name of the pediatric trial
Modified-IB1001 Modified-IXINITY	Modified IXINITY after manufacturing modification
Former-IB1001 Former-IXINITY	Original IXINITY before manufacturing modification
PK	Pharmacokinetics
PTP	Previously Treated Patient; Previously Treated Subject
rFIX	Recombinant Factor IX
SAE(s)	Serious Adverse Event(s)
SAR(s)	Serious Adverse Reaction(s)

1. Executive Summary

a) Clinical Program

The totality of the clinical efficacy data came from a completed pivotal, phase 1/2/3 clinical trial (IB1001-01) and two ongoing clinical trials. One of the ongoing trials is a continuation of the completed pivotal trial using modified-IXINITY and the second is an ongoing deferred, pediatric trial (IB1001-02). The safety database included all subjects who received IXINITY. A total of 92 subjects provided consent to screen for the pivotal trial. The pivotal trial enrolled 77 subjects, aged 7-64 years old and all subjects received an original version of the product, referred to as former-IXINITY throughout this review (see the chemistry section for more product specific details). All were male except one female carrier enrolled in the Surgery Substudy. The pediatric trial, still ongoing, has enrolled nine subjects, three aged < 6 and six between 6 and 12, inclusive. Seven pediatric subjects transitioned to modified-IXINITY; demographics of these pediatric subjects were Asian (n=6) and Caucasian (n=1), all male (n=7), and aged 6-14 years.

Study Design

The pivotal clinical trial for IXINITY was a combined phase 1/2/3, prospective, multicenter, international trial. A Surgery Substudy was also included. Primary objectives of the trial were to evaluate pharmacokinetics, safety, immunogenicity, and efficacy in previously treated patients. Phases included PK and Repeat PK, Treatment, Continuation, and ongoing Modified Phases. General criteria for all phases included severe and moderately severe Hemophilia B, coagulationFactor IX (FIX) ≤ 2 IU/dL), age ≥ 12 years except for subjects in Treatment Phase in the U.S. who could be as young as 5 years old, previous FIX treatment ≥ 150 ED, negative for FIX inhibitors (< 0.6 Bethesda Units), and no allergy to hamster proteins.

The PK Phase employed a randomized, double-blind, crossover design using 75 ± 5 IU/kg of former-IXINITY or a previously licensed comparator rFIX. An optional repeat PK Phase with former-IXINITY was offered at 3-6 months. A former-IXINITY recovery study was required for those who did not participate in the PK Phase.

Treatment Phase was an open-label, uncontrolled trial of safety and efficacy of former-IXINITY. Treatment Phase lasted 6 months, was planned for 50 exposure days (ED) per subject in ≥ 50 subjects, and had a planned sample size of ≤ 80 subjects. The initial routine treatment dosing regimen was 50-75 IU/kg twice weekly. Bleeding episodes were treated with an initial intravenous dose of 50-100 IU/kg and repeated as needed. Safety endpoints included product tolerance, adverse events (AEs), and immunogenicity. Efficacy endpoints included subject's rating of efficacy, investigator's rating of efficacy, change in pain, change in swelling, time to cessation, and number of infusions required.

Continuation Phase was an optional, open-label, uncontrolled phase that evaluated long-term safety and effectiveness for ≥ 100 ED in ≥ 50 subjects. Continuation Phase was initiated with former-IXINITY but subjects were transitioned to modified-IXINITY (refer to Modified Phase below). Immunogenicity was monitored along with safety and efficacy data.

Surgery Substudy was an open-label, uncontrolled study with former-IXINITY. Subjects did not have to participate in other treatment phases of the trial although they did have to

complete the PK Phase or PK Recovery Study. Bolus or continuous infusion were permitted. Efficacy and safety, including immunogenicity and vital signs, were monitored. Three male subjects with severe Hemophilia B, recurrent hemarthroses, and FIX levels between 2-8% were included in the surgery study (FIX levels of 2.8%, 5-6%, 8%; inclusion criterion of FIX level ≤ 2 IU/dL was waived because of clinical severity). One subject continued into the Treatment Phase as a protocol deviation.

Modified Phase was defined as Continuation Phase with modified-IXINITY. The objectives of the Modified Phase were to assess recovery of modified-IXINITY following a single infusion, anti-CHOP immunogenicity testing, anti-FIX immunogenicity testing, and safety. All subjects transitioning to modified-IXINITY were required to have assessment of in vivo recovery of modified-IXINITY before entry and every 6 months after initial dosing.

Population and Disposition

A total of 92 subjects provided consent to screen for the pivotal trial. The trial enrolled 77 subjects, aged 7-64 years old. All were male except one female carrier enrolled in the Surgery Substudy. Comparability and nonclinical testing were conducted and showed that former- and modified-IXINITY were similar except for post-modification removal of host cell proteins and decreased immunogenicity. Based on these results, efficacy and general safety results were extrapolated from the pivotal trial that used former-IXINITY to modified-IXINITY.

The total number of subjects exposed to former-IXINITY in the pivotal trial was 77 subjects, with 9641 infusions administered and mean exposure of 138 exposure days (ED). There were 55 subjects with ≥ 50 ED and 45 subjects with ≥ 100 ED. In the PK Phase, exposures ranged from 3,818-10,808 IU per subject. In Treatment and Continuation Phases, total exposure was 9395 days as of 2013-03-01. Mean exposure for combined treatment and continuation phases was 138 days (median 128 days). Mean exposure for routine and on-demand groups were 149 days (median 136 days) and 84 days (median 94 days), respectively. In the Surgery Substudy, exposure ranged from 4-16 days.

For Modified Phase, 17 subjects on routine treatment were exposed to 854 infusions of modified-IXINITY (median 58 ED, range 4-106 ED). Mean dose for routine treatment was 4,632 IU per ED (IU/ED), and mean dosing interval was 3.5 days (median 3 days, range 0-14 days). Mean doses for the two subjects were 2730 and 2294 IU/ED. Dosing intervals ranged from 1-13 days.

In the Modified Phase of the pediatric trial, seven pediatric subjects received 370 infusions of modified-IXINITY for routine treatment. Median exposure was 50 ED (range 26-99 ED), mean dose was 1,558 IU/ED, and mean dosing interval was 3.7 days (median 4 days, range 0-8 days).

Efficacy Analysis

Efficacy for treatment of bleeding episodes was studied in 68 subjects in the Treatment Phase with former-IXINITY. Routine and on-demand treatment regimens were chosen by 61 and 12 subjects, respectively, at some point during the investigation (some switched between regimens with former-IXINITY and are represented twice). A total of 508 bleeding episodes were reported, with 286 breakthrough bleeds in the routine group

and 222 bleeds in the on-demand group. For all bleeds (n=508), bleeding resolved after one or two infusions in 71% (n = 360) and 13% (n = 65) of bleeds, respectively. At least five infusions were required in 5% (n = 24) of bleeds, typically related to trauma, target joints, muscle bleeds, or surgery not included in the Surgery Substudy. The mean dose for treatment of bleeding episodes was 60 IU/kg. Hemostatic efficacy was rated by subjects as excellent or good in 84% of all bleeds treated, 13% were rated fair, and 3% were rated poor. An excellent response was defined as a dramatic response, a good response required an additional infusion for resolution, fair was defined as a probable response requiring several additional infusions, and a poor response showed no improvement.

In the Surgery Substudy, 16 males aged 12-56 years of age, underwent 19 major operations with former-IXINITY. The female subject was a protocol deviation and not included in the efficacy analysis because her FIX levels were too high. Target FIX levels and effective hemostasis were achieved by both bolus and continuous infusion regimens during and after surgery. Blood loss was as expected (68%) or less than expected (32%) in all surgical procedures. No instance of poor hemostasis or intraoperative transfusion was recorded.

Because of the comparability chemistry manufacturing and controls and pharmacology pharmacokinetic data, clinical efficacy was extrapolated from former-IXINITY to modified-IXINITY. The observed bleeding rate with modified-IXINITY in an early interval analysis of seven subjects from the ongoing Modified Phase of the pivotal trial was stated by Cangene as consistent with prior observations. Interval data from infusion logs and diaries indicated that four new bleeding episodes in three subjects occurred during the Modified Phase. One bleed was likely a spontaneous breakthrough bleed and one bleed in another subject was post-traumatic. Two bleeds in one subject may have been due to compliance issues. Efficacies of on-demand treatment for two bleeding episodes in two subjects with available diaries were assessed as good by both subjects. Early interval investigator ratings for treatments with modified-IXINITY in the pivotal trial found them to be effective in all reported instances.

Recovery studies in the pivotal trial 6 months after modification (n=7) showed median recovery of 85% for modified-IXINITY (vs. 89% for former-IXINITY; mean 79% vs. 94%). Mean recovery in the Modified Phase in the pediatric trial for modified-IXINITY (n=4) was 52% (vs. mean 53% for 3 of those 4 subjects pre-modification).

Safety Analysis

Safety was evaluated by assessment of adverse experiences, vital signs, clinical laboratory results, and immunogenicity. Particular attention was paid to adverse events (ARs) of special interest known for the FIX class including: thrombogenicity, immunogenicity, anaphylaxis, hypersensitivity, inhibitor formation, and nephrotic syndrome.

Adverse Reactions and Serious Adverse Reactions

In the Treatment and Continuation Phases with former-IXINITY, 14 adverse reactions (ARs) occurred in 6 of 77 subjects (9% of subjects; 3% of events were reactions). There were no deaths or related serious adverse reactions. No anaphylactic reactions or nephrotic syndrome were reported. The most common ARs were headaches with 5

events in 2 (3%) of 77 subjects. ARs were mild (n = 7, in five subjects) or moderate (n = 7, in two subjects). No severe ARs were reported.

Adverse Events and Serious Adverse Events

A total of 449 AEs were reported in 75% (58/77) of subjects. Analysis of laboratory values and vital signs for former-IXINITY did not demonstrate any safety signals. The most commonly reported AEs were: headaches (17%), arthralgia (16%), pyrexia (13%), nasopharyngitis (12%), and limb injury (10%). Headaches and nasopharyngitis were the most common AEs reported in the on-demand group (33%). Thrombotic events, hypersensitivity, anaphylaxis, and nephrotic syndrome were not reported. The overall frequency of adverse events per injection was < 1%.

Serious adverse events (14 in 10 subjects) occurred during Treatment and Continuation Phases, were all considered unrelated by Cangene, and included: diverticulitis, injury, wound infection, hematoma, abdominal pain, and mental status change associated with injury. The clinical reviewer also agreed that all serious adverse events were unrelated to former-IXINITY.

Surgery Substudy

The Surgery Substudy revealed no safety signals. Ten of 16 subjects experienced 33 adverse events. There were no deaths or serious AEs. AEs were mild in 25 events and moderate in 7. One subject required a transfusion in the postoperative period, which was considered expected given the difficulty and extent of the operation. This challenging case was a bilateral knee replacement; one knee required extensive bone and soft tissue manipulation. Blood loss during surgery was approximately 300 mL, which was as expected. Hemoglobin declined from 14.6 to 6.0 gm/dL over two days. During this period, the subject maintained FIX levels between 53% (lowest trough) and 156% (highest peak). The bleeding was anticipated pre-operatively, ultimately required four transfusions over 2 days, but still was reported as an AE. Pyrexia was the most common adverse event, seen in 18% of subjects.

Modified Phase

In Modified Phase with modified-IXINITY, 14 AEs were observed among 17 patients. None of the events to date were considered related to the product by Cangene. Ten events in four subjects were mild and four events in two subjects were moderate. The moderate events included diverticulitis, migraine, limb injury, and nephrolithiasis. There were no serious or severe AEs.

Adverse Events of Special Interest - Immunogenicity

Immunogenicity data from the pivotal trial were available for 68 of 77 subjects, including data for all 17 subjects who transitioned to modified-IXINITY™. Immunogenicity data from the ongoing pediatric trial were available for 9 of 9 subjects, 7 of whom transitioned.

Anti-CHOP Antibodies were positively identified in 20 subjects (29% of 68 total) who received original-IXINITY™, with another 11 (16%) counted as indeterminate because of baseline positivity (n=2), non-specific antibody binding (n=5), isolated positive results (n=3), or limited follow-up (n=1). Titers of anti-CHOP antibody ranged as high as 316885. These subjects have been followed for up to 3 years (median 414 days) without related clinical adverse findings or laboratory sequelae. No excess allergic

reactions, rashes, anaphylaxes, renal diseases, or arthropathies were identified during Treatment Phase. No subject who transitioned to the modified-IXINITY™ has substantially increased their titer or developed new anti-CHOP antibodies.

Inhibitory Anti-FIX Antibodies were not reported at any time in either former- or modified-IXINITY™ clinical trials. No patterns of adverse reactions related to the non-inhibitory anti-FIX antibodies have been identified in any of the subjects.

Non-Inhibitory Anti-FIX Antibodies were detected in 23 subjects who received former-IXINITY during the pivotal trial. Five of 23 subjects were positive at baseline. Therefore, 18 of 77 subjects (23%) developed new non-inhibitory antibodies. In three of the subjects in the pivotal trial, the non-inhibitory factor IX antibodies were persistent, while in the remainder the antibodies were sporadic and non-persistent. In the pediatric trial while receiving former-IXINITY, three of nine subjects (33%) were transiently positive for non-inhibitory anti-FIX antibody.

Out of 17 subjects in the pivotal trial who transitioned to modified-IXINITY™, anti-FIX antibody data were available for the first 12 subjects enrolled. Of these 12, only one subject demonstrated one positive result for a transient non-inhibitory anti-FIX antibody, followed by multiple negative results. All seven transitioned pediatric subjects in the ongoing pediatric study were consistently negative for anti-FIX antibodies. No patterns of adverse reactions related to the non-inhibitory anti-FIX antibodies have been identified in any of the subjects.

Adverse Events of Special Interest – Thromboembolic Adverse Events

No thromboembolic adverse events were reported in any subject at any time during the clinical trial. Monitoring of D-dimer, prothrombin fragments 1 + 2, and thrombin-antithrombin complex during the PK Phase did not reveal any simultaneous positivity of all three markers.

Companion review of the kit

A series of kit presentations were introduced that include one or more vials of drug product carrying the same strength, a vial adapter, a prefilled syringe of diluent, and a 20-mL administration syringe. The purpose of the kit is to allow pooling of vials, as more than half of subjects in the pivotal trial pooled vials. Risk and hazard analysis found the kit to be acceptable as the design was consistent with the market and used industry-standard components. The vial adapter with the filter, sterile administration syringe and the infusion set are all 510(k) cleared earlier by the Center for Devices and Radiologic Health and the intended use for each of these devices is the same as that previously approved. Labeling and patient instructions have been updated and should address any associated risks. No human factors studies were requested.

b) Pediatrics

The non-pivotal pediatric study is deferred and ongoing, but included here in support of the safety and decreased immunogenicity of modified-IXINITY. The pivotal clinical trial with former-IXINITY included twelve subjects ≤ 18 years old, including nine subjects < 16 and six between 12 and < 16 years. Nine subjects between 7 and 17 years had ≥ 100 ED. This data was presented before PeRC on 2014-06-18. Because 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 was recommended. The committee found the assessment acceptable and agreed with deferral of studies for subjects 0 to < 12 years old. Recovery of modified-IXINITY in the ongoing pediatric trial for subjects < 12 years old was lower, to be reviewed in the final study report. Pediatric subject exposure in the pivotal trial is provided in the following table.

Pediatric Exposure to former-IXINITY from Pivotal Trial IB1001-01

Patient ID	*Age (years)*	*Data Contribution to Study Analyses*	*Total Exposure Days*
(b) (6)		PK, safety, efficacy	188
		PK, safety, efficacy	221
		PK, safety, efficacy	211
		PK, safety, efficacy	171
		Safety, efficacy	267
		Safety, efficacy	67
		Safety, efficacy	49
		Safety, efficacy	125
		Safety, efficacy	123
		Safety	1
		Safety, efficacy, surgery	141
		Safety, efficacy, surgery	138

In the Modified Phase of the pediatric trial, seven subjects received 370 infusions of modified-IXINITY for routine treatment. Median exposure was 50 ED (range 26-99 ED), mean dose was 1,558 IU/ED, and mean dosing interval was 3.7 days (median 4 days, range 0-8 days).

Pediatric Requirements

Modified Phase in the pediatric trial is ongoing and analysis will be submitted with the final study report. The trial enrolled nine pediatric subjects, three aged < 6 and six between ages 6 and 12. Seven pediatric subjects transitioned to modified-IXINITY; demographics of these seven pediatric subjects were Asian (n=6) and Caucasian (n=1), all male.

Other Special Populations

There are no recommendations for any special populations. No subjects > 65 years old were studied.

PMCs and/or PMRs

Cangene has committed to perform and complete a deferred pediatric study for subjects under 12 years old.

Bioresearch Monitoring

In consultation with the medical reviewer, five sites participating in pivotal trial were selected for Bioresearch Monitoring inspections by the Division of Inspections and Surveillance. Study subject enrollment and previous inspection history were among the factors used to select the inspected sites. The inspections focused on specific questions concerning the study protocol and the comparison of data submitted in the BLA to

source documents. Inspection outcomes did not reveal significant problems that impacted the clinical data submitted to BL STN 125426/0.

Overall Comparability Assessment

IXINITY is effective for control and prevention of bleeding episodes and perioperative management. In 77 subjects, development of inhibitory antibodies and anaphylaxis were not observed. Modified-IXINITY was shown to be comparable to former-IXINITY.

Labeling considerations

Review of labeling is complete. The prescribing information includes a statement describing the different recovery results in different age strata. The labeling recommends measurement of FIX levels in patients and individual dose adjustments. Recovery of modified-IXINITY in ongoing trials has trended lower than pre-modification, but the numbers are small. It is possible that modification of the labeling will be needed once the final study reports become available.

Recommendation:
From the clinical reviewer perspective, the application for IXINITY has shown acceptable safety and efficacy of the current product for the indications claimed. Labeling review is complete. The clinical reviewer recommends approval.

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 (FIX) resulting in bleeding secondary to abnormal clot formation. Hemophilia B occurs in approximately 1 in 50,000 people and constitutes 20% of the total hemophilia A and B population. The disease presents virtually exclusively in males but is also 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. Long-term consequences include hemophilic arthropathy, a potentially devastating complication which can lead to disability or joint replacement.

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

- Treatments for hemophilia B require replacement with FIX. FIX formulations include human plasma products such as fresh-frozen plasma or prothrombin complex concentrates. FIX products, either plasma derived or recombinant, are commercially available. Recombinant factor IX (rFIX) 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 rFIX product was BeneFIX, which was approved in 1997. There are two plasma derived FIX products approved: Alphanine and Mononine.
- During the review process, Rixubis rFIX 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.
- Inhibitor formation is one of the most important consequences of treatment with allogeneic or recombinant clotting factors. Inhibitory antibody formation is associated with decreased efficacy of treatment, along with adverse reactions such as anaphylaxis or nephrotic syndrome. Inhibitors manifest in hemophilia B in approximately 1-4% of patients. Hypersensitivity reactions occur in approximately 50% of patients with inhibitors, especially patients with major FIX gene deletions. Also, inhibitor formation is accompanied by severe allergic reactions and nephrotic syndrome in 50% of patients afflicted.

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

- 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. during July 2012 because some subjects developed titers to Chinese hamster ovary host cell proteins. Some of the titers were high and/or rising.
- 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 FIX product. After review, some subjects were allowed to stay on former-IXINITY at the discretion of investigators and subjects. [Source #01, 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. IXINITY is produced in Chinese Hamster Ovary (CHO) cells and has a primary amino acid sequence identical to the Thr148 allelic form of plasma-derived FIX. 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

- BeneFIX is also made in CHO cells.
- Amendment 39 explains the characterization of the impurities in former-IXINITY. A number of steps were taken. (b)(4)

(b)(4)

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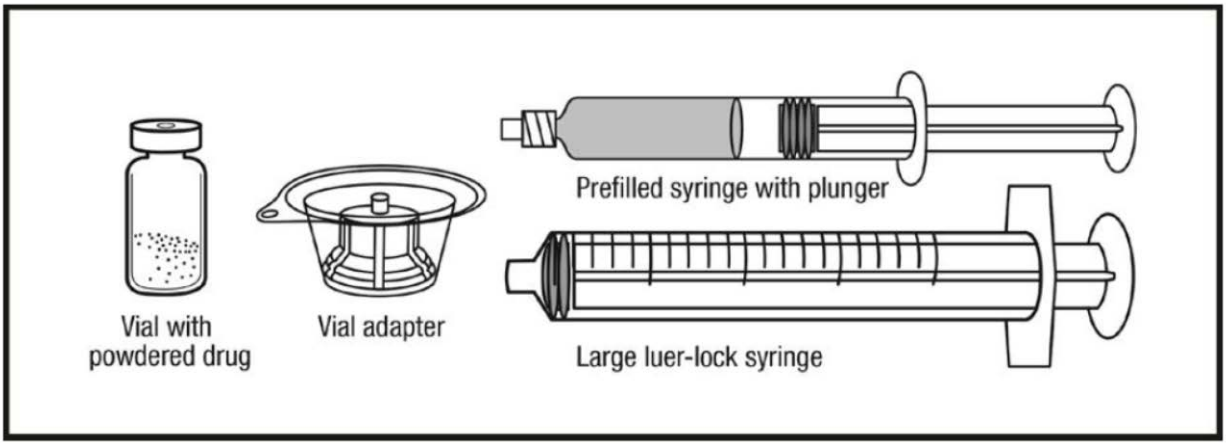
- Several steps in the manufacturing process have been introduced to reduce potential immunogenicity. A (b)(4) step reduced levels of host cell proteins. Comparability testing indicated that the modified-IXINITY was physiochemically and biologically similar to former-IXINITY. Similarities were demonstrated in areas of potency, identity, purity/(b)(4) , and impurities. (b)(4) A new host cell protein (b)(4) has been validated that is more specific to the IXINITY host cell line than the previous (b)(4) HCP assays. The (b)(4) specificity of the new(b)(4) has been shown to cover impurities present in former-IXINITY that were associated with high rates of antibody formation in trial subjects.
- Process Validation document, p. 6/20, discusses the drug substance and product FIX validations. (b)(4)

Kit Risk and Hazard Analysis

DMPQ has evaluated the kit and are satisfied with the application. No human factors studies are needed for this specific patient population.

The new kit includes a vial of lyophilized drug product, a vial adapter, a prefilled syringe of diluent, and a larger administration syringe. The prefilled syringe comes with the plunger attached.

Figure 1



The purpose of the kit is to allow pooling of multiple vials, since more than half of subjects in IB1001-01 pooled vials for administration. A risk and hazards analysis was performed as per (b) (4) The risk level ranking in the analysis was found to be acceptable because the design of the kit is consistent with the market and uses industry-standard components. The syringes use standard Luer-lok connectors. The target

population is already performing intravenous injections and already pooling product. The drug is administered by patients and caregivers, in the hospital, clinic, or home setting. Risks and hazards were evaluated using impact, severity, and probability generated from internal and external sources. As a result of the analysis, labeling and patient instructions have been updated and should lower any associated risks.

4.2 Assay Validation

- Please refer to the memo from the product reviewer.
- Note that (b)(4) are reported as negative.
- A new anti-CHOP (b)(4) was developed using a (b)(4) to increase the sensitivity of the assay.

4.3 Nonclinical Pharmacology/Toxicology

- Please refer to the memo from the product reviewer regarding comparability and bridging studies between original and modified product.
- Please refer to the memo from the nonclinical toxicologist regarding comparability and immunogenicity testing in animals. This toxicologist memo was written during the review of resubmission #1 after the first CR letter. Pharmacokinetic comparison between former-IXINITY and modified-IXINITY in rats showed comparable exposure as measured by AUC after a single intravenous injection. Immunogenicity comparison between the versions in rabbits demonstrated decreased incidence and titers of anti-CHOP antibodies in the modified product, which was evidence of decrease immunogenicity with the current product. Testing for extractable and leachable substances revealed results that were acceptable without substantial safety concerns.

  Testing of AUC in rats was performed in two groups of 15 rats each. Animals in the former-IXINITY received approximately 10% higher doses on average. Results adjusted for dose were found to be non-inferior (ratio of geometric means = 91%, above the 80% threshold) and bioequivalent (lower bound of 95% confidence interval for the ratio = 85%, also above the 80% threshold).

  Testing of immunogenicity in rabbits was performed in cohorts of 12 animals per sex per group. Animals were dosed twice weekly for 9.5 weeks. No significant differences in clinical findings, weights, or laboratory suggested drug-related toxicity. No differences in toxicokinetics were found. Rabbits that received current product demonstrated lower incidence (1 vs. 23 out of 24) and lower median titers (117 vs. 14809) of anti-CHOP antibodies [Source #02, p. 8].

4.4 Clinical Pharmacology

- Please refer to the memo from the clinical pharmacologist.
- See Memo Sections 6.1.11.1 for the pivotal trial and 6.2.11.1 for the pediatric trial.

Figure 2: Summary of Factor IX Results (%) for Initial Recovery Studies in Former- vs. Modified-IXINITY

Visit	Statistics	Original Product	Polished Product
Pre-infusion*	N	7	7
	Mean	3.7	3.0
	StdDev	1.70	3.32
	Min	1	0
	Median	3	2
	Max	6	8
15 minutes post-infusion	N	7	7
	Mean	89.4	73.7
	StdDev	21.76	14.55
	Min	58	59
	Median	83	73
	Max	118	95
1 hour post-infusion	N	7	7
	Mean	81.7	68.1
	StdDev	21.82	14.83
	Min	52	53
	Median	75	67
	Max	115	89
24 hours post-infusion	N	7	7
	Mean	25.7	22.7
	StdDev	6.73	4.89
	Min	18	18
	Median	24	21
	Max	35	30

[Source #01, p. 53]

4.5 Statistical

- Please refer to the memo from the statistical reviewer. Initial labeling and data submissions used square-root transformed numbers 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.
- Ultimately, agreement was reached to use normal scale for mean annual bleeding rates.

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

5.1 Review Strategy

The review strategy reflects the introduction of a manufacturing change during evaluation of the application. Evaluations of pharmacokinetic profiles, safety, and efficacy were performed on the product before the manufacturing change. After the manufacturing change, chemistry and nonclinical animal *[Memo Section 4.3]* showed that modified-IXINITY was chemically similar, toxicokinetically similar, and less immunogenic than former-IXINITY. A manufacturing change of this magnitude would not typically mandate repeat of a pivotal efficacy trial, so the applicant was told that a repeat efficacy trial was not required. Pharmacokinetic recovery, general safety, and immunogenicity data from the modified product were analyzed.

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

- See Review Memo Section 12.

5.3 Table of Completed 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.

Particularly important sources of data for review of IB1001-01 were the *Consolidated Report*, the *Supplemental Clinical Study Report*, and *Summary of Clinical Safety,* and multiple iterations of the *Immunogenicity Risk Assessment*. Because IB1001-02 is ongoing, limited information is available and primarily reflects Modified Phase. Data are still being collected under two ongoing protocols in Modified Phase. For Modified Phases in IB1001-01 and -02, primary sources have been the *Supplemental Clinical Study Report* and the periodic *Immunogenicity Risk Assessment* documents.

Table 1: Status of Clinical Trials for Former- and Modified- IXINITY

	Pivotal Trial (IB1001-01)	***Pediatric Trial (IB1002-02)***
PK Phase (former-IXINITY)	N=32;14 underwent repeat PK	N=9
Treatment Phase / Continuation Phase (former-IXINITY)	N=68 58 began on routine treatment regimen, increased to 61 during the trial. 9 began on-demand regimen, increased to 12 during the trial. 1 not assigned	9 subjects assigned to routine treatment regimen
Surgery Substudy (former-IXINITY)	N=18 enrolled 1 surgery cancelled, 1 female carrier N=16 for efficacy analysis	0
Modified Phase (# transitioned to	N=17, ongoing 15 began on routine treatment,	N=7, ongoing

modified-IXINITY)	2 on on-demand or targeted prevention	

5.4 Consultations

- No internal or external consultations were requested by the clinical team. An advisory committee was not convened.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

The original BLA, dated 2012-03-30, included data from the pivotal clinical trial IB1001-01. The application received a complete review letter on 2013-02-01 because of manufacturing deficiencies that stemmed from presence of CHO proteins and clinical concern over immunogenicity to those CHO proteins. Resubmission #1, dated 2014-01-27, included additional data from IB1001-01 and added data from ongoing pediatric clinical trial IB1001-02. Resubmission #1 received a complete review letter on 2014-07-29 because of CMC deficiencies. Resubmission #2, dated 2014-10-28, added information from ongoing trials IB1001-01 and IB1001-02, particularly immunogenicity data.

6.1 Clinical Trial #1: IB1001-01

The final protocol Amendment 11 was titled *Phase I/II/III Pharmacokinetic and Outcome Study of Recombinant Factor IX Product, IB1001, in Subjects with Hemophilia B*. The protocols were conducted under one IND.

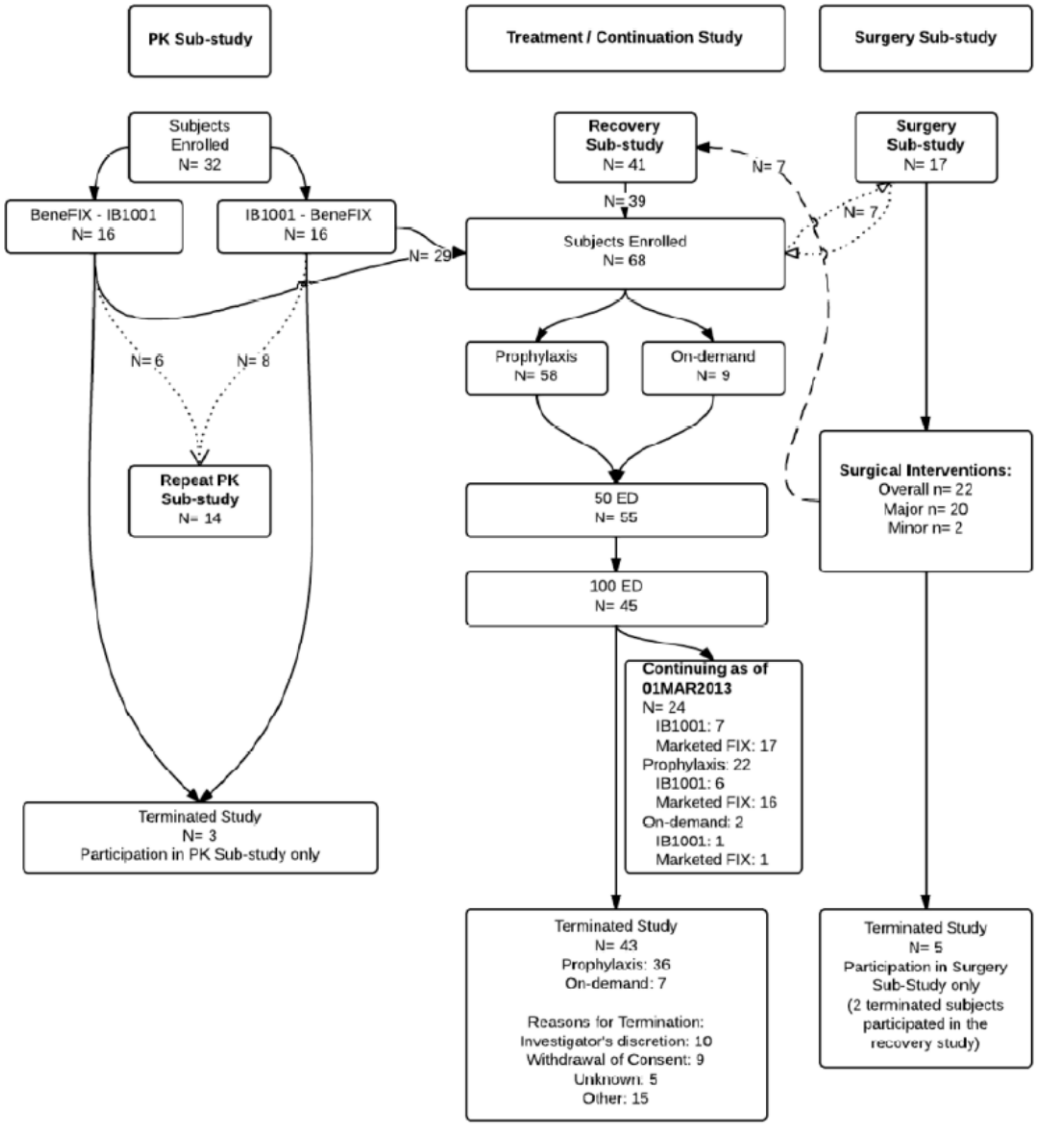
6.1.1 Objectives

Primary objectives of the IB1001-01 phase 1/2/3 studies were to evaluate the pharmacokinetics, safety, and efficacy of former-IXINITY for routine and on-demand treatment. For the current application with modified-IXINITY, the efficacy objective was limited to on-demand treatment as the prophylaxis claim was no longer available because of exclusivity restrictions. 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 #16, p. 20]. For the study of modified-IXINITY, objectives were to assess (1) drug recovery following a single infusion, (2) anti-CHOP immunogenicity, (3) anti-FIX immunogenicity, and (4) clinical safety. [Source #01, 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. *[See Figure 2]*

Figure 3. Most Recent IB1001-01 Study Design



[Source #13, Figure 1, p. 5]

The design of the various phases of IB1001-01 is presented below.

1. PK Phase: Study of BeneFIX vs. IXINITY, Recovery Study, or Repeat PK Study
    - The original PK Phase employed a randomized, double-blinded, crossover design. Following a ≥ 5 day washout period, levels of FIX and inhibitors were measured [*Surveillence* in Memo Section 6.1.7]. Subjects were randomized to BeneFIX or former-IXINITY [*Treatments* in Memo Section 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-IXINITY PK Phase was offered at 3-6 months after the end of the initial PK Phase. The participants received IXINITY only.
- An IXINITY recovery assessment (Recovery Study) 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. IXINITY was then infused.

2. Treatment Phase: The pivotal Treatment Phase with former-IXINITY was a non-randomized, open-label, uncontrolled clinical trial to study safety and efficacy of routine and on-demand treatment. Treatment Phase lasted 6 months and was planned for approximately 50 exposure days per subject in ≥ 50 subjects. Subjects could start with routine or on-demand therapy per subject and investigator preferences, and could switch between regimens again as per preference. The treatment regimens are given in Memo Section 6.1.4 and monitoring schedule in Memo Section 6.1.7.
3. Continuation Phase: The Continuation Phase with former-IXINITY optionally followed Treatment Phase and also was a non-randomized, open-label, uncontrolled clinical trial. Continuation Phase was intended to evaluate long-term safety and effectiveness of routine and on-demand treatment for > 100 exposure days in ≥ 50 subjects. Anticipated duration was one year or up to protocol completion. Participants and investigators could again select routine or on-demand therapy, and switch as desired. Continuation Phase with former-IXINITY was terminated in the United States and many other jurisdictions, but was allowed to continue in some countries. Continuation Phase with modified-IXINITY is ongoing under Modified Phase [see below] and most active subjects will transition to current product (modified-IXINITY).
4. Surgery Substudy: The 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 collection of sufficient PK and safety data. [Source #10, p. 766]
5. Modified Phase: The Modified Phase was added under Protocol Amendment 11 [Source #10, p. 912]. Subjects receive modified-IXINITY in the updated Continuation Phase for ≥ 12 months. Prior to initiation of dosing, a PK recovery study with modified-IXINITY is performed. The date of the modified-IXINITY recovery study is Day 0 (or Day 1) for planning subsequent visits. After 12 months of Continuation Phase, participants can continue further until end of study in 2015-07. [Source #01, p. 30]

6.1.3 Population

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 FIX inhibitors ≥ 0.6 Bethesda Units and allergy to hamster proteins.

1. PK Phase: Almost all countries required that subjects enrolled in the PK Phase be ≥ 12 years old and ≥ 40 kg body weight, except France which required subjects be ≥

18 years old. 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 former-IXINITY. 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 inclusion criteria for general study entry, and had to participate in the PK Phase 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 Phase or 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 modified-IXINITY.
5. Continuation Phase Study of Modified-IXINITY:

   Inclusion criteria were similar to the criteria in Amendment 7, 2010-01-25. No new subjects are enrolled; all are transitioned from former-IXINITY or marketed product within the existing protocol.

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 former-IXINITY or BeneFIX, and then crossed over. Participants in the recovery study received a single intravenous dose of 75 ± 5 IU/kg of former-IXINITY.
2. Treatment Phase: With former-IXINITY, the initial routine 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 former-IXINITY. Repeat doses could be administered as needed to achieve hemostasis. For routine treatment, 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 #20, p. 14]
3. Continuation Phase: Treatments were the same as Treatment Phase.
4. Surgery Substudy: Bolus or continuous infusion of IXINITY 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. No surgery subject has received modified-IXINITY.
5. Modified Phase: Modified Phase is defined as Continuation Phase with modified-IXINITY. The dose for the recovery study required before transition was 75 IU/kg of modified-IXINITY. No comparator was administered. Dosing regimens for Modified Phase were 50-75 IU/kg for routine and 50 IU/kg initial dose 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 former-IXINITY studies were performed at 23 sites in 7 countries: U.S.A, U.K., France, Italy, Israel, Poland, and, India. For Modified Phase, nine sites in the U.S., U.K., and India contributed data for 17 subjects transitioned to modified-IXINITY [Source #09, adapted from p. 9].

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 routine treatment or spontaneous bleeding during on-demand was monitored. Adverse events, tolerance, and compliance were monitored with clinic visits and subject-reported diaries. In the routine treatment group, inhibitory (neutralizing) and non-inhibitory antibodies were measured after the first 5 exposure days and every 3 months [Source #08, p.26]. 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: Former-IXINITY 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 #16, 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.
    - For subjects who continued on former-IXINITY 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 former-IXINITY 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 #01, 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 IXINITY

treatment. Vital signs were monitored routinely and additionally appropriate to the amount of bleeding.

5. Modified Phase:

- For PK of modified-IXINITY, recovery was the only parameter investigated. This is performed at transition and every 6 months thereafter. [Source #01, p. 43]
- Modified Phase:
  - Safety monitoring includes clinical safety, laboratory findings, and immunogenicity results. Immunogenicity testing included antibodies against CHOP and is performed more frequently during the first 3 months, and every 3 months thereafter [Source #08, p. 4].
  - The schedule of assessments for Modified Phase is provided in Table 1. End-of-study assessment, either completion or withdrawal, is provided in the supplemental study report, p. 34.
  - During first 12 months of treatment with modified-IXINITY, assessments are every 3 months. Those who choose to continue ≥ 12 months until 2015-07 are assessed every 6 months.

Table 2. Table of Assessments for modified-IXINITY 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 #01, p. 32]

Table 3. 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 #01, p. 34]

6.1.8 Endpoints and Criteria for Study Success

The primary endpoints for the entire trial were to evaluate safety and efficacy of IXINITY.

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 FIX in the initial recovery study is calculated as C(max) minus baseline levels.
2. Treatment Phase: Efficacy endpoints for bleeding episodes were defined separately for episodes that occurred during routine and during on-demand treatment. If subjects switched regimens, separate rates were calculated for each regimen. Endpoints were 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. Tolerance and compliance were assessed from subject-reported diaries.
    - The *Response* document in Amendment 28 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.

- Safety endpoints included product tolerance, adverse events, adverse reactions, and immunogenicity. Events within 72 hours of infusion were collected. An adverse event was defined as "any untoward medical occurrence in a subject who is administered clinical study material. The occurrence of this event does not necessarily have a causal relationship with study product." Causality was classified using the ICH Classification. Adverse reactions were defined as adverse events with causality assessed as definitely related, probably related, or possibly related. Adverse events assessed as unrelated or probably not related/remotely related were reported as unrelated.
- For treatment of bleeding episodes, clinical endpoints gathered from subjects and investigators were used. These endpoints included subject's rating of efficacy, investigator's rating of efficacy, change in pain, change in swelling, time to cessation, and number of infusions required. Quality of life measurements are made using the EQ-5D in subjects ≥ 12 years old [Source #23, 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 modified-IXINITY assessed recovery only. After a washout period of ≥ 5 days, FIX levels were determined preinfusion, and after a single intravenous infusion of 75 IU/kg of modified-IXINITY at 15 minutes and hours 1 and 24. For modified-IXINITY, recovery was calculated as C(max) - baseline FIX. [Source #01, p. 30]
    b. Definitions for immunogenicity are given in Memo 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 routine treatment 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 a 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 analysis 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 routine vs. on-demand treatment 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 modified-IXINITY, 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 routine 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 former-IXINITY are also listed for subjects who receive modified-IXINITY.

6.1.10 Study Population and Disposition

- A total of 92 subjects provided consent to screen for IB1001-01. [Source #13, p.13]. 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).
- All data in the original amendment resubmission #1, with data lock of 2013-03, were with the product before the additional (b)(4) was added. Safety and efficacy were determined during clinical trials using former-IXINITY. 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 comparability results, a repeat clinical trial was not required and efficacy was to be extrapolated from former-IXINITY to modified-IXINITY [Source #17].

1. Pharmacokinetic Phase: PK phase has been completed. Subjects were eligible to proceed to Treatment Phase or Surgery Substudy. All but three PK subjects went on to other phases.
2. Treatment Phase: The plan was to enroll ≤ 80 subjects overall with 60 in routine and 20 on-demand groups, for 50 evaluable routine and 18 evaluable on-demand subjects. Eight subjects were in other phases but did not continue with Treatment Phase (three in PK and five in Surgery).
    - 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 former-IXINITY, 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 former-IXINITY. Subjects either exited the study or stayed on study with transition to a marketed FIX product. [Source #01, p. 28]
    - Disposition in other countries is briefly discussed in Memo Section 2.6.
3. Continuation Phase: Subjects were originally allowed to receive treatment with former-IXINITY in Continuation Phase for as desired, until end of study. After clinical hold was lifted, 24 subjects agreed to remain in Continuation Phase with the eventual goal to transition to modified-IXINITY. Of the 24 subjects, 17 subjects transitioned to marketed product and 7 subjects stayed on former-IXINITY, presumably due to availability and cost of marketed product outside the U.S. [Source #04, data lock of 2013-03]
4. Surgery Substudy: The study planned to enroll ≥ 5 subjects and collect ≥ 10 major surgeries. Five subjects exited Trial IB1001-01 after their surgery. Seven subjects came to Surgery Substudy from Treatment Phase. Five subjects entered Treatment Phase after surgery. No subjects received surgery with modified-IXINITY.
5. Modified Phase:
    - The ITT population for modified-IXINITY consisted of subjects who received at least one dose of modified-IXINITY.
    - Modified Phase and the study as a whole will end 2015-07.
    - A total of 26 subjects had received modified-IXINITY as 2014-12-18 [Source #09], 17 under IB1001-01 and 9 under IB1001-02. Monitoring of other subjects is ongoing.

6.1.10.1 Populations Enrolled/Analyzed

A total of 77 subjects were enrolled in the Phase 1/2/3 clinical trial. One of the 77 was a female carrier enrolled in the Surgery Substudy. Her FIX levels were higher than allowed by protocol, so she was excluded from efficacy analysis [Source #16, pp. 74]. Table 12 [Source #20, p. 28] provides addition details on subject disposition. Estimated bleeds in the 6 months prior to enrollment are given in the following table:

Table 4. 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 #16, 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 58 subjects enrolled in the Treatment Study who were preassigned to receive routine treatment and 9 preassigned to receive on-demand. One subject was not assigned to a group. One subject was waived into the Treatment Phase after participation in the Surgery Substudy, with a FIX level of 8% but clinically severe hemophilia B with repeated hemarthroses and severe hemophilic arthropathy [Source #16, pp. 62]. Mean age was 30 years old. 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. Because subjects could switch regimens, over the length of investigation 61 subjects received routine treatment and 12 received on-demand. A total of 9395 exposure days were experienced by the 68 subjects, with 58 subjects on routine treatment 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) [Source #01, 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 #24, 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 [Source #16, Section 11.1.3, p. 63; Source #24, p. 3].
4. Surgery Substudy: A total of 17 subjects were enrolled. One of the 17 was a female carrier. Her FIX levels were higher than allowed by protocol, so she was excluded from efficacy analysis. Three male subjects were waived into the

surgery study with FIX levels between 2-10% (2.8%, 5-6%, 8%) but with clinical evidence for severe hemophilia B with recurrent hemarthroses. One subject with clinically severe hemophilia continued into Treatment Phase [Source #36, p. 34.] A total of 16 subjects (5 planned) were included for analysis, with 19 major surgery cases (10 planned) were performed and included [Source #16, pp. 74-79 (bottom numbers)]. Mean age was 33 years. There was one subject who enrolled in the Substudy but improved and surgery was cancelled. This person was included in the analysis of safety. Continuous infusion was used in six procedures and bolus in 13 procedures. Five subjects participated in the Surgery Substudy only.

5. Modified Phase: As of 2014-07-17, 17 subjects from IB1001-01 have transitioned to modified-IXINITY from former-IXINITY. The most interim recent data are from 2015-01-19. Data from ongoing pediatric study IB1001-02 are in Memo Section 6.2.10.1.

- 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 nine subjects < 16 and six between 12 and < 16 years. Nine subjects between 7 and 17 years have ≥ 100 exposure days.

Table 5. 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 #24, p. 4]

6.1.10.1.1 Demographics

- Table 13 [Source #20, p. 33] provides addition details on subject demographics.
- Clinical Trial IB1001-01 [Calculated with JReview]

Study Type	PK / Safety / Efficacy
Study Design	Multicenter, prospective, open-label,

	uncontrolled, nonrandomized
Ages Studied	0 years to < 18 years, adults
Subjects (n), Age at First Enrollment	12
0 to < 6 years	0
6 to < 12 years	3
12 to < 16 years	6
16 to < 18 years	3
Centers (n)	23, including adults
Countries (n)	7: UK, France, Italy, Israel, Poland, USA, India; including adults
Race, N (%)	77 (100%) total; 9 (100%) pediatric < 16 years
Caucasian	61 (79%); 2 (22%) pediatric
Asian heritage	8 (10%); 3 (33%) pediatric

- Clinical Trial IB1001-02 [Source #20]

Study Type	PK / Safety / Efficacy
Study Design	Multicenter, prospective, open-label, uncontrolled, nonrandomized
Ages Studied	0 years to < 12 years
Subjects (n), Age at First Infusion	9
0 to < 6 years	3
6 to < 12 years	6
12 to 16 years	0
Countries (n)	2 (United Kingdom and India as of Amendment 5);
Race, N (%)	9
Caucasian	2 (22%)
Asian heritage	7 (78%)

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, but the prophylaxis indication was blocked by exclusivity. The following efficacy analysis discusses primarily on-demand and perioperative treatment. Efficacy endpoints for bleeding episodes emphasized degree of hemorrhage control, whether the bleeds were breakthrough or spontaneous. Degree of hemorrhage control was 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 #16, p.34]

6.1.11.1 Analyses of Primary Endpoint(s)

1. PK Phase: IXINITY 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.

Table 6: Summary of PK Parameters - BeneFIX vs. former-IXINITY

PK Parameter*	BeneFIX Mean ± SD	Former-IXINITY 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 #16, Table 11:22, p. 96]

2. PK Phase, Repeat: Pharmacokinetic profiles with IXINITY were stable when repeated and reassessed after 6 months. [Source #16, p. 76]

3. Treatment Phase: The ITT population consisted of subjects with severe hemophilia B (FIX levels ≤ 2%), aged 7-64 years, with ≥ 150 exposure days, most with bleeds in ≥ 2 major joints. Analyses were performed on the ITT population. The number of subjects in the table below reflects the group that the subject was in at the time of the bleed, and differs from the group at start of the trial.

Table 7. Efficacy of IXINITY in Treatment Phase

	Routine (n = 61)	On-Demand (n = 12)
Treatment Duration (months) **Mean (± SD)** **Median (range)**	 17.9 (± 9.6) 16.2 (2.4-39.6)	 15.9 (± 11.5) 14.1 (2.3-36.9)
Dose per Infusion (IU/kg) Mean (± SD) Median (range)	 55.0 (± 12.8) 53.0 (26.1-80.2)	 60.0 (± 18.2) 59.3 (23.9-94.1)
Total ABR Mean (± SD) Median (range)	 3.55 (± 7.19) 1.5 (0.0-47.5)	 16.14 (± 11.83) 16.4 (0.0-39.4)

[Source #22, p. 2]

a. Aggregate: A total of 508 bleeding episodes were reported, with 286 breakthrough bleeds in the routine treatment group and 222 bleeds in the on-demand group. In the entire group (n=508), bleeding resolved after one or

two infusions in 71% (n = 360) and 13% (n = 65) of bleeds, respectively. At least five infusions were required in 5% (n = 24) of bleeds, typically related to trauma, target joints, or muscle bleeds. The highest numbers of infusions (20 and 24 infusions) were required in surgical procedures not included in the Surgical Substudy. Mean dosing for treatment of bleeding in the on-demand group was 60 IU/kg [Source #20, p. 43]. Hemostatic efficacy was rated by subjects as excellent or good in 84% of all bleeds treated. Efficacy was rated as fair in 13% and poor in 3% of bleeds. Only 17% of subjects (n = 2) assigned to on-demand treatment had zero bleeds. [Source #20, p. 37]

b. Routine Treatment: The median annualized bleeding rate (ABR) during prophylaxis was 1.5 (mean 3.55). Seven subjects on routine treatment had > 10 bleeding episodes; in some, most were post-traumatic. Subject (b) (6) experienced 35 bleeding episodes, 32 which were post-traumatic. There were others with a similar pattern. Breakthrough bleeding occurred in 69% of subjects on routine treatment (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.

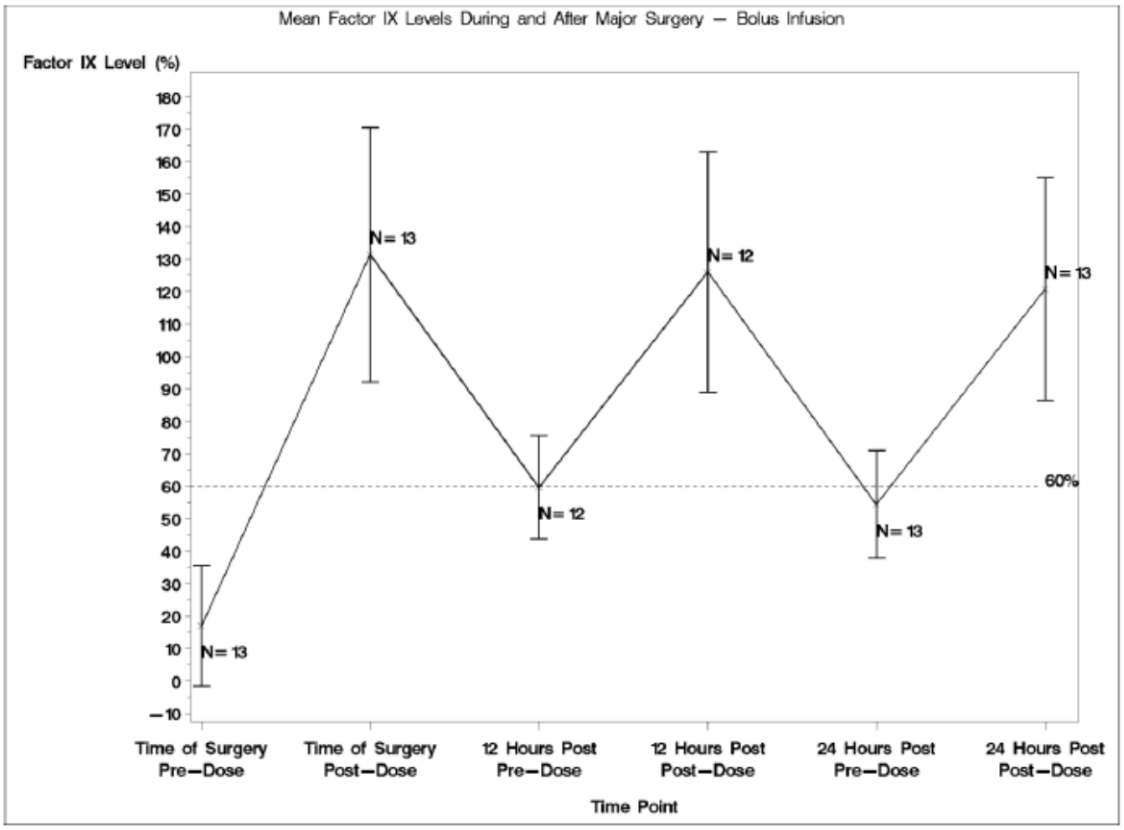
c. On-Demand: The median number of bleeding episodes was 16 per year (mean 16, range 0-39) [Source #16, p. 85]. IXINITY was effective for treatment of bleeding episodes as assessed by times for resolution of the bleed, associated pain, and swelling. The number of subjects who chose on-demand assignment was relatively small. Of those fewer subjects, investigators ranked one subject's overall treatment as partially effective (12.5% of subjects), and all other treatments were ranked as effective [Source #16, p. 85]. Subjects in the on-demand group rated the efficacy of treatment for spontaneous bleeds as excellent or good in 24% and 56%, respectively. [Source #16, p. 86]

   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% (n = 169 bleeds) or 5% (n = 25) of bleeding episodes, 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.

4. Surgery Substudy: Sixteen subjects, aged 12-56 years of age, underwent 19 major operations. Note that in some places, the documents indicate 17 subjects and 20 major surgeries, but one subject was excluded because she was a carrier. Thus, there were 16 evaluable subjects with 19 evaluable major

surgeries. Target FIX levels were achieved by both bolus and continuous infusion regimens [Source #23, 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%.

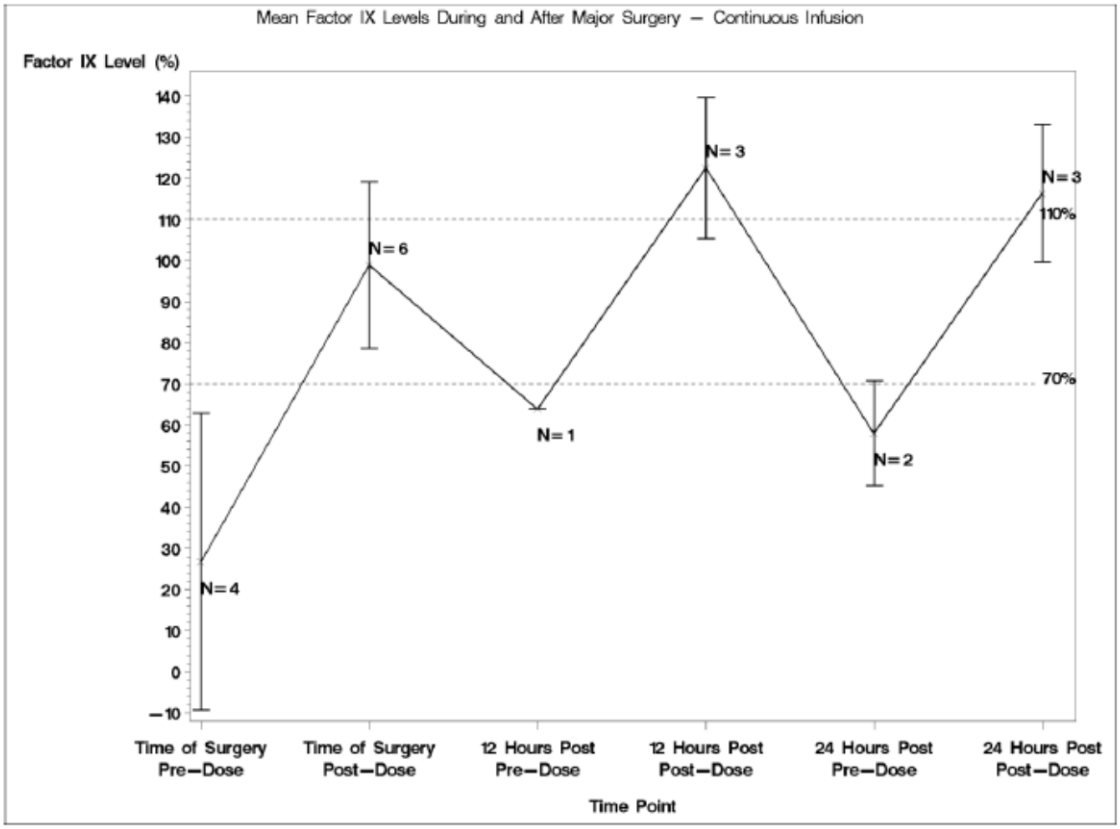
Figure 4. Mean Factor IX Level During and After Major Surgery - Bolus Infusion



[Source #16, 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 5. Mean Factor IX Level During and After Major Surgery - Bolus Infusion



[Source #16, 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 #16, p. 87]

Table 8. 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 #20, adapted from Table 9, p. 23]

5. Modified Phase: Efficacy was not formally studied for modified-IXINITY. Because of the convincing analytical and nonclinical comparability data, a repeat efficacy study was not required. Any efficacy data available would be strictly anecdotal. In addition, all subjects who received modified-IXINITY were on routine treatment, whereas the approvable indications are for on-demand treatment of bleeding and perioperative management. The sample size of 17 subjects is too small to draw definitive conclusions, efficacy is addressed only in 7 subjects and the duration of follow up is short. The observed bleeding rate with modified-IXINITY in seven subjects summarized by the applicant is consistent with prior observations, although details are lacking. The investigators judged modified-IXINITY to be effective as shown in the following table.

Table 9: Interval Investigator Ratings for Treatment with modified-IXINITY™

Exposure Days	*Investigator Rating of Efficacy*	*N (%)*
5 EDs	Effective	6 (100%)
	Partially effective	0 (0%)
	Not effective	0 (0%)
	Not applicable	0 (0%)
	Requires further evaluation	0 (0%)
1 Month	Effective	7 (100%)
2 Months	Effective	5 (100%)
3 Months	Effective	6 (100%)

Data from infusion logs and diaries indicated that four new bleeding episodes in three subjects occurred during the modified-IXINITY 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 routine treatment as assessed by investigators was effective for all subjects at 5 exposure days and at months 1, 2, and 3 of modified-IXINITY 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 #01, pp. 12, 55-57]

One subject missed two visits. Another subject missed a number of infusions and experienced two bleeds; the relationship of the bleeds to the compliance issue is speculative. Also, safety endpoints were missing in 50% of subjects (5/10). [Source #01, p. 49]

Table 10: Table of Deviations

Rating	**Deviation Code**	**Overall N* = 10**

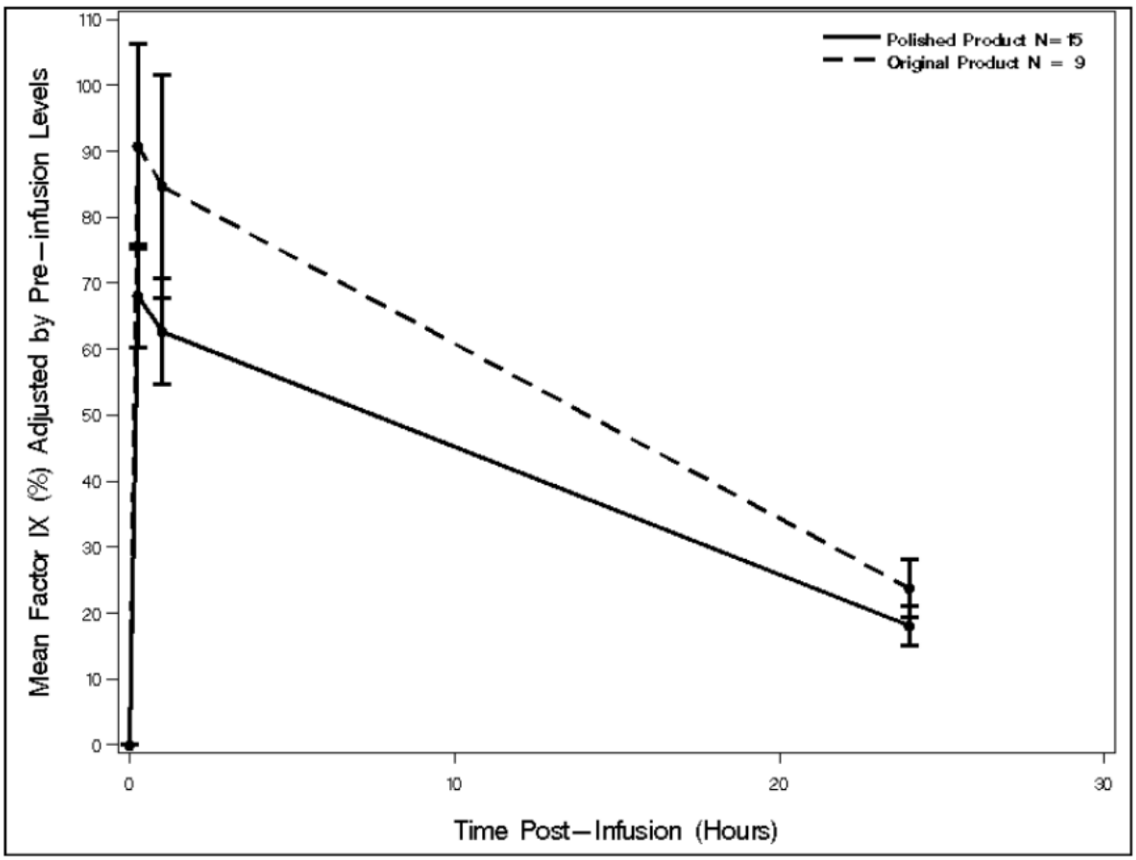
		N (%)
Major	3. Study Visits	2 (20.0%)
Minor	4. Subject non-compliance	3 (30.0%)
	6. Safety endpoint assessments	5 (50.0%)
* Total number of protocol deviations		

[Source #01, p. 49]

PK on Modified-IXINITY: Recovery parameters for former- and modified-IXINITY were similar. See Review Memo Section 4.4.

Recovery PK data were gathered in Modified Phase in the pivotal trial. At the beginning of transition to modified-IXINITY, after a washout period of ≥ 5 days, FIX blood levels are taken prior to, and after infusion of 75 ± 5 IU per kilogram at 15 minutes, 1 hour, and 24 hours. Recovery data with modified-IXINITY were available at transition (n=15/17 subjects interpretable) and 6 months after (n=7/17 subjects). Of the 15 subjects with interpretable data, 9 had values from former-IB1001-01. Median recovery, at 15 minutes adjusted for baseline, for IXINITY pre-modification and post-modification baseline and 6 months, were 86%, 70%, and 81%, respectively (mean 90.7%, 68.2%, and 74.9%, respectively). Median recovery, at 1 hour adjusted for baseline, for IXINITY pre-modification and post-modification baseline and 6 months, were 79%, 64%, 69%, respectively (mean 84.6%, 62.7%, 64.0%, respectively). See Figures 7 and 8. [Source #33, pp. 7-8]

Figure 6: Recovery with Original and Modified-IXINITY in Pivotal Trial (Mean and STD)



[Source #33, p. 7]. Fuzzy quality is from original image.

Reviewer comment: Because the values tended to merge, it is possible that the differences in immediate (15 minute) levels were more technical than immunologic or metabolic.

Figure 7: Summary of Factor IX Results (%) for Original and Modified-IXINITY Recovery in Pivotal Trial

Time-point	Statistic	Original IB1001	Polished IB1001	
		Initial	Initial	6 Months
Pre-infusion	N	9	15	7
	Mean	3.7	2.7	4.1
	StdDev	1.50	2.52	2.34
	Minimum	1	0	2
	Median	3	2	4
	Maximum	6	8	8
15 minutes post-infusion	N	9	15	7
	Mean	94.4	70.9	79
	StdDev	23.54	15.41	19.84
	Minimum	58	53	49
	Median	89	72	85
	Maximum	132	101	96
1 hour post-infusion	N	9	15	7
	Mean	88.3	65.4	68.1
	StdDev	25.61	16.07	18.80
	Minimum	52	44	40
	Median	82	66	73
	Maximum	134	94	91
24 hours post-infusion	N	9	14	N/A
	Mean	27.4	21	N/A
	StdDev	6.98	6.18	N/A
	Minimum	18	13	N/A
	Median	29	19	N/A
	Maximum	37	31	N/A

A result below the limit of quantitation recorded as <1% at pre-infusion was set to 0 for this summary table.
N/A: not applicable as 24-hour time point was not required for 6-month recovery.

6.1.11.3 Subpopulation Analyses

- 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 #20, p. 44]. Full PK analysis was not done for any subjects < 12 years old (actually < 14 years old) [Source #34, p. 7].

6.1.12 Safety Analyses

6.1.12.1 Methods

- Pivotal safety analysis included full protocol data from 2009-02 to 2013-03. Safety data collection was extended and reviewed to 2014-07-17 for IB1001-01 and to 2014-10-24 for IB1001-02 [Source #09, p. 4]. Particular attention was paid to generally recognized, important safety issues including thrombogenicity, immunogenicity, anaphylaxis, hypersensitivity, inhibitor formation, viral and prion transmission, and nephrotic syndrome.
- Known toxicities from the FIX clotting factor class include inhibitor development; hypersensitivity, allergy, and anaphylaxis; nephrotic syndrome; and thromboembolic complications. Anaphylaxis and nephrotic syndrome rarely occur in the absence of inhibitors.
- Adverse reactions (ARs) are defined as adverse events (AEs) that were considered related to the test article. Criteria for assessment of seriousness, severity, and causality of adverse events were provided [Source #01, p. 41]. Adverse events were considered related if not categorized as unrelated, probably not related, or remotely possibly related. Relatedness for many types of acute events was defined as an occurrence within 24 hours of product administration. Long-term safety was defined in populations with 50 or 100 exposure days.
- 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 FIX are categorized similarly with an additional layer for inhibitory and noninhibitory.

6.1.12.2 Overview of Adverse Events and Reactions

Exposure

- The total number of subjects exposed to the test article former-IXINITY in IB1001-01 was 77 subjects, with 9641 infusions (median 116 infusions) administered and overall mean exposure of 138 exposure days (ED). There were 55 subjects with ≥ 50 ED and 45 subjects with ≥ 100 ED.
- 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 and Continuation Phases: Total exposure was 9395 days as of 2013-03-01. Mean exposure for this phase was 138 days (median 128 days). Mean exposure for routine and on-demand treatment groups were 149 days (median 136 days) and 84 days (median 94 days), respectively.
    - Surgery Substudy: Exposure ranged from 4-16 days, with cumulative doses up to 144,397 IU.
    - Modified Phase: Exposure included the doses for the initial and 6-month recovery studies, and doses for continuation with post-modification IXINITY. Mean exposure from the single dose for initial recovery study

was 75.28 IU/kg (n=17, median 75 IU/kg, range 75-78.78 IU/kg). Mean exposure from the 6-month recovery study was 74.69 (n=7, median 75 IU/kg, range 72.8-75 IU/kg). Two subjects missed their 6-month recovery study. For Modified Phase continuation, 17 subjects received 843 infusions.

Fifteen subjects on routine treatment had median exposure of 58 ED (range 4-106 ED). Mean dosing interval was 3.5 days (SD ±1.4 days, median 3 days, range 0-14 days). Mean dose was 4,631.9 IU/ED (SD ±2887.53 IU/ED). Mean cumulative dose per subject on routine treatment was 306,693.4 IU (SD ±353,503.05 IU).

Two subjects who received on-demand and targeted preventive treatment had exposures of 9 and 36 ED. Dosing intervals ranged from 1-13 days. Mean doses for the two subjects were 2730 and 2294 IU/ED. Cumulative doses for the subjects were 24,570 and 82,584 IU.

Dose consumption was stable in all subjects, allowing for vial potency.

- Exposure data from Modified Phase was available until 2014-04. 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 #01, pp. 60-61]

Adverse Reactions - Former-IXINITY:

- Adverse reactions are drug-related adverse events. For former-IXINITY, adverse reactions were determined in 14 of 449 AEs (3% of events were reactions) in 6 of 77 subjects (8% 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 = 7, in five 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.
- Allergic symptoms reported during Treatment Phase included asthma, rash, cough, seasonal allergies, nausea, chest tightness, and chest pain. Asthma and seasonal allergies were assessed as pre-existing and ongoing, and unrelated to treatment.

Table 11. Adverse Drug Reactions With Former-IXINITY 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%
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 #16, adapted from 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, but was removed by the reviewer as an adverse event.

> *<u>Reviewer comment:</u> An information request was sent to the applicant. They indicated that there was nothing special about the one noninhibitory antibody case that resulted in it being reported as related, just that it was at the discretion of the investigator (even though the final decision should be that of the sponsor/applicant). This will be removed as a related adverse reaction and deleted from the label.*

<u>Adverse Events - Former-IXINITY:</u>

- Overall, 449 adverse events were reported in 58 subjects (75% of subjects) in Trial IB001-01 through pivotal Treatment and Continuation Phases. There were 14 serious events, all considered unrelated. No deaths were reported. For routine treatment, 347 events were reported in 49 subjects. All 14 serious events occurred in the routine treatment 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%). Headaches and nasopharyngitis were the most common AEs reported in the 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%) [Source #13, Table 8, pp. 28-36; Source #16, p. 256]. For routine treatment, 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.

- 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 16 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. This challenging case was a bilateral knee replacement; one knee required extensive bone and soft tissue manipulation. Blood loss during surgery was approximately 300 mL, which was as expected. Hemoglobin declined from 14.6 to 6.0 gm/dL over two days. During this period, he maintained FIX levels between 53 (lowest trough) and 156% (highest peak). This degree of bleeding was anticipated pre-operatively, ultimately required four transfusions over 2 days, but still was reported as an AE [Source #36, pp. 5, 51-52]. Pyrexia was the most common event, seen in 18% of subjects.
- For the entire Trial 1001-01, from beginning through Modified Phase date 2015-07-17, 567 adverse events were recorded.

Adverse Events - Modified-IXINITY

- Safety data was collected to 2014-07-17 for Trial IB1001-01. Safety data from Trial IB1001-01 were available for 12 of 17 subjects transitioned from former- to modified-IXINITY as of 2014-07-17. [Source #08, p. 4]
- The clinical and laboratory safety profiles are consistent with former-IXINITY. A total of 14 AE were observed. Ten events in four subjects were mild and four events in two subjects were moderate. The moderate events were diverticulitis, migraine, limb injury, and nephrolithiasis. 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 #01, pp. 62-64]

Table 12. Summary of Adverse Events by Preferred Term, modified-IXINITY

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#01, adapted from pp. 63-64]

- 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 clinical trial.

6.1.12.4 Nonfatal Serious Adverse Events

- No events of anaphylaxis or serious allergic reactions were reported in any subject at any time.
- No related serious adverse reactions were reported. There were 14 serious adverse events in ten subjects, all during Treatment and Continuation Phases, all considered unrelated by the applicant. The reviewer agreed that all serious adverse events were unrelated to IXINITY, save for one which was unlikely to be related. 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. All SAEs are detailed in Table 11.
    - One subject suffered a spinal fracture that required open reduction, related to a car incident and surgery precipitated by a seizure. Seizures were a pre-existing condition. [Source #16, p. 366].
      Reviewer comment: *This was considered unrelated to IXINITY by the reviewer.*

Table 13: Serious Adverse Events in Pivotal Trial of IXINITY

SAE, Severity, Subject	Event	Hospitalization	Relatedness	Resolution	Date of prior treatment	Date of AE beginning	Withdrawn/last treatment
SAE #1, Moderate Subject #1	Fainted, fell, hit head, hematoma	Hospitalization Treated with IXINITY	Applicant: Unrelated Reviewer: Unrelated	Resolved	2011-09-27	2011-09-30 (3 days after prior treatment)	Not specified in narrative. Not on withdrawn list.
SAE #2, Moderate Subject #2	Abdominal pain, acute diverticulitis	Hospitalization	Applicant: Unrelated Reviewer: Unrelated	AE resolved Pain ongoing	2010-07-23	2010-07-26 (3 days after prior treatment)	IXINITY continued, stayed in study. Not on withdrawn list.
SAE #3, Severe Subject #2	Fever, abdominal pain, acute diverticulitis	Hospitalization	Applicant: Unrelated Reviewer: Unrelated	Resolved	2013-01-25	2013-01-16 (9 days before prior treatment): Fever, pain, antibiotics for 1 week 2013-01-28 (3 days after prior treatment): Fever, hypotension	Not specified in narrative. Not on withdrawn list.
SAE #4, Mild Subject #3	Motorcycle accident, foot laceration	Hospitalization	Applicant: Unrelated Reviewer: Unrelated	Resolved		2010-01-16	IXINITY continued , stayed in study. Withdrawn 2010-11-03 (10 months after SAE), lack of compliance.
SAE #5, Severe Subject #4	Periprosthetic fracture	Hospitalization	Applicant: Unrelated Reviewer: Unrelated	Resolved with sequelae	2012-06-26	2012-06-21 (5 days before prior treatment): Fracture 2012-07-25 (1 month after prior treatment): Surgery, [? No treatment during surgery]	Not specified in narrative. Not on withdrawn list.
SAE #6, Severe Subject #5	Hip injury	Hospitalization	Applicant: Unrelated Reviewer: Unrelated	Resolved	Not specified	2012-04-26: Jumped into water 2012-04-27: Severe hip pain 2012-04-30: Hospitalized, probable hemarthrosis, received marketed product by mistake	IXINITY continued , stayed in study. Not on withdrawn list.
SAE #7, Moderate Subject #6	Arm injury	Hospitalization	Applicant: Unrelated Reviewer: Unrelated	Resolved	2012-06-30	2012-07-01 (1 day after prior treatment): Injured with baseball bat, discharged with marketed product	Not specified in narrative. Not on withdrawn list.
SAE #8, Moderate Subject #6	Arm injury	Hospitalization	Applicant: Unrelated Reviewer: Unrelated	Resolved	Not specified	2012-07-12: Reinjured left arm lifting object, hematoma, treated and discharged with marketed product	Not specified in narrative. Not on withdrawn list.
SAE #9, Moderate Subject #7	Abdominal pain	Hospitalized	Applicant: Unrelated Reviewer: Unlikely	Resolved	Not specified	2011-01-23: Abdominal pain for 1 week	IXINITY continued , stayed in study. Withdrawn 2011-09-26 (8 months after SAE), moving out of country.
SAE #10, Moderate Subject #8	Head injury, altered mental status	Hospitalized	Applicant: Unrelated Reviewer: Unrelated	Resolved	Not specified	2011-11-10: Hit in eye with hockey puck 2011-11-11: Increased somnolence	IXINITY continued , stayed in study. On withdrawn list, no date or reason specified.

SAE #11, Severe Subject #9	Spinal injury	Hospitalized	Applicant: Unrelated Reviewer: Unrelated	Ongoing	2011-08-13	2011-08-15 (2 days after prior treatment): Seizure (had history of), spine injury, surgery	Not specified in narrative. Withdrawn 2011-10-05 (< 2 months after SAE), lack of compliance.
SAE #12, Life-threatening Subject #9	Wound infection	Hospitalized	Applicant: Unrelated Reviewer: Unrelated	Resolved.		2011-09-09: Readmitted with wound infection. Surgery performed. Treated with marketed product.	Not specified in narrative. Withdrawn 2011-10-05 (< 2 months after SAE), lack of compliance.
SAE #13, Severe Subject #10	Femur fracture	Hospitalized	Applicant: Unrelated Reviewer: Unrelated	Resolved	Not specified	2012-06-12: Probable fracture through chronic osteomyelitis. Had amputation.	Not specified in narrative. Not on withdrawn list.
SAE #14, Mild Subject #10	Wound infection	Hospitalized	Applicant: Unrelated Reviewer: Unrelated	Resolved	Not specified	2012-08-09: Wound infection. Wound debridement. Treated with marketed product.	Not specified in narrative. Not on withdrawn list.

6.1.12.5 Adverse Events of Special Interest (AESI)

- **Immunogenicity:** Two types of immunogenicity of special interest in Trial IB1001-01 were development of antibodies against Chinese hamster ovary host cell proteins (anti-CHOP) and against FIX (anti-FIX). See Memo Section 6.2.12.5 for similar discussion of ongoing pediatric Trial IB1001-02.
    - *Anti-CHOP Antibodies (Anti-CHOP):*

      Reviewer comment: The product primarily responsible for the discussion of anti-CHOP immunogenicity will no longer be manufactured, and is included for historical perspective. The current product (modified-IXINITY) is not known to be similarly immunogenic.

      - Immunogenicity data from Trial IB1001-01 were available for 68 of 77 subjects, including data as of 2014-07-17 for 17 of 17 subjects who transitioned to modified-IXINITY. As of 2014-10, these 68 subjects have at least one time point assessed beyond screening. Data is not available for 9 of 77 subjects because (a) three subjects were in the pharmacokinetic segment only, (b) three subjects were in the surgery substudy only, and three subjects discontinued or withdrew early. [Source #09, p. 7]
      - For former-IXINITY, by data lock date of 2013-03-01, a final total of 20 out of 68 subjects (29%) demonstrated development of anti-CHOP antibodies [Source #07, p. 4]. Conversely, 37 subjects (54%) remained negative for anti-CHOP [Source #09, p. 4]. The remaining 11 subjects (16%) had indeterminate results (n=11) that included positive baseline (n=2), (b)(4) nonspecific reactivity (n=5), isolated or sporadic positive results (n=3), or insufficient follow up (n=1).
          - Two subjects (3% of 68 total) were positive for anti-CHOP at screening.
              - Subject (b) (6) was positive at screening but no initial titer was done. Subsequent titer range was 88-344 (with intermittent, nonconsecutive, nonspecific (b)(4) binding detected). [Source #07, pp. 47-48]
              - Subject (b) (6) was considered positive, even with conflicting screening results, as one screening result was > 100.
          - Three subjects (4%) had isolated or sporadic positive results.
              - Subject (b) (6) was negative at entry and exit, but had two nonconsecutive positive results.
              - Subject (b) (6) had a positive result with four subsequent negative results.
              - Subject (b) (6) had a positive result with surrounding visits having nonspecific reactivity.
      - No clinical effects of the anti-CHOP antibodies were identified on efficacy or adverse event profiles while subjects received former-IXINITY. No excess allergic reactions, rashes, anaphylaxes, renal diseases, or arthropathies were identified during the treatment phase of the trial. Subjects who elected to remain on study were followed with enhanced monitoring, including

immunogenicity testing every 3 months. Subjects who developed anti-CHOP antibodies have been followed for up to 3 years without detection of clinical or laboratory sequelae. Subjects have been followed after seroconversion for a median of 414 days [Source #13, p.85].

- In Treatment/Continuation Phase during which there was 406 events reported, 224 of the events were in anti-CHOP negative subjects.
- Detailed narratives for subjects who were anti-CHOP positive were presented [Source #09, Section 3.1.1.1.1, pp. 9-16.]

Reviewer comment: The materials were reviewed and reveal no pattern of adverse event or reaction that identified a clinical pattern of adverse experience linked to anti-CHOP antibody formation. Even if a pattern had been discerned, the relevance would have been unclear since the current product shows no evidence of anti-CHOP immunogenicity.

- Between the Treatment and Continuation Phases with former-IXINITY and Modified Phase with modified-IXINITY, an additional (b)(4) step was added to manufacturing to remove host cell proteins, the host cell proteins (HCPs) were characterized, and an assay to monitor the HCPs was validated. Nonclinical comparability studies showed that modified-IXINITY was comparable to former-IXINITY in physiochemical, biological, and pharmacokinetic characteristics.
- Table 12 presents the categorization of anti-CHOP results from IB1001-01 and transitions to modified-IXINITY.

Table 14. Summary of Anti-CHOP Results from IB1001-01 Clinical Trial Subjects

Anti-CHOP Classification	**N (%)**	**Subjects** (See Table 1 in immunogenicity document.)
Negative	37 (54%)	Includes 10 subjects transitioned to modified-IXINITY.
Indeterminate	11 (16%)	Includes 3 subjects transitioned to modified-IXINITY.
Positive Seroconversion	20 (29%)	Includes 4 subjects transitioned to modified-IXINITY.

- In eight of nine subjects with high titers during treatment with former-IXINITY, anti-CHOP titers have decreased. One of those that decreased became negative. The one subject whose titer did not decrease was stable. [Source #09, p. 9]

- During Modified Phase, 17 subjects in Trial IB1001-01 transitioned from former-IXINITY to modified-IXINITY by 2014-07-17. None of these subjects increased or developed anti-CHOP titers. Ten subjects that were negative remained negative. Four subjects were positive after former-IXINITY; two displayed decreased titers after transition and two are too early in their course to assess. Three subjects were indeterminate before and after transition. [Source #09, p. 9]

- See Memo Section 6.2.12.5 for information about anti-CHOP activity in ongoing Pediatric Trial IB1001-02.

o *Anti-FIX Antibodies:*

- No FIX inhibitors (neutralizing antibodies) have been identified in any subject, including 62 subjects in Trial IB1001-01 on routine treatment and 56 subjects on routine treatment for more than six months [Source #09, p. 26]. Transient noninhibitory anti-FIX antibodies were found in 30% of subjects (23/77), 18 of whom who were negative and 5 positive at baseline [Source #09, p. 26]. No safety concerns have been identified in the subjects' adverse event profiles related to the noninhibitory anti-FIX antibodies. Treatment doses remained stable.

  Reviewer comment: Absence of safety signal related to noninhibitory antibody is expected and reflects literature and Agency experience, as clinical significance of this finding has not been established.

  - One case of noninhibitory anti-FIX antibody was reported as an adverse reaction. This is a reporting anomaly, see note in Memo Section 6.1.12.2.
  - Details for subjects who were positive for noninhibitory anti-FIX antibody were presented [Source #09, Section 3.1.3.1, pp. 20, 26-27].
  - Most (15/18) of the newly developed noninhibitory anti-FIX antibody responses in Trial IB1001-01 were transient [Source #09, Section 10.6, Annex 6, pp. 98-117].
  - Three subjects (3/18) in Trial IB1001-01 had more persistent responses with newly developed, noninhibitory anti-FIX antibodies.
    - Subject (b) (6) had adverse events of hypertension, shoulder pain, and one instance of abdominal pain and diarrhea. All events were moderate and all were considered unrelated. There was no obvious temporal relationship with antibody formation.
    - Subject (b) (6) had a large number (n=33) of adverse events. These included dizziness, joint pain, infections, headache, dizziness, skin redness, and itching. All events were mild or moderate, and all were considered unrelated. There was no obvious temporal relationship with antibody formation.

      Reviewer comment: The redness and itching occurred once and did not recur, so unlikely was related to drug. The other events were intermittent over a long course of treatment and either are common adverse experiences in the general population (back pain) or common adverse experiences in the target population (arthralgia).

    - Subject (b) (6) also had a large number of adverse events (n=18). These included severe arthritis, moderate hepatic cirrhosis, moderate hypertension, and mild instances of fever, sore throat, chest congestion, and postoperative pain. All events were considered unrelated. The moderate hypertension had a temporal relationship with the noninhibitory antibodies. The other adverse events had no temporal relationship with antibodies.

Reviewer comment: Although not possible to exclude that the hypertension is related to the drug, hypertension is very common and there is no pattern for occurrence of this adverse experience with the test article.

- See Memo Section 6.2.12.5 for information about anti-FIX activity in ongoing Pediatric Trial IB1001-02.

- **Thrombogenicity:** Thrombogenicity was an adverse event of special interest 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 in any subject at any time during the trial [Source #16, p. 106].

6.1.12.6 Clinical Test Results

In the pivotal trial with former-IXINITY, analysis of laboratory values and vital signs did not demonstrate any safety signals.

One subject demonstrated low platelets and hemoglobin related to a car accident and surgery precipitated by a seizure, also after treatment with BeneFIX at the hospital. Seizures were a pre-existing condition. [Source #16, p. 366].

Reviewer comment: The reviewer concludes that the hematological abnormalities could not be considered related to product.

Modified-IXINITY: Laboratory analysis of the seven subjects transitioned by 2014-02-28 did not demonstrate any safety signals. [Source #01, 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. Subjects at one site were withdrawn after the investigator decided to join a competing trial. 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 #16, pp. 58-59]

6.1.13 Study Summary and Conclusions

Overall, the safety and efficacy profiles of the current version of IXINITY are considered acceptable and expected, and the benefit-risk ratio is favorable.

Efficacy Conclusions:

- The BeneFIX/former-IXINITY PK study showed no significant differences in AUC or C(max). The repeat PK study at 6 months revealed comparable parameters. Recovery of modified-IXINITY showed no substantial difference from former-IXINITY.
- Subjects in the ITT population for the Treatment Phase were aged 7-64 years and most had experienced bleeds in ≥ 2 large joints. Most subjects of the ITT population were on routine treatment. A small fraction was treated on demand. However, a claim for prophylaxis indication is blocked by another product's

exclusivity rights, so indications are for on-demand treatment and prevention of bleeding and for perioperative management.

- Efficacy was established using former-IXINITY, before the introduction of the additional (b)(4) step. A manufacturing change of this smaller magnitude would not normally require a new efficacy trial. Comparability testing indicated that the products were similar, so efficacy for the current version of the product was extrapolated from the legacy product. For routine treatment, the mean annualized bleeding rate for subjects was 3.55 ± 7.19 (median 1.52). routine treatment regimens were usually rated by investigators as effective with a few partially effective. No treatment was rated as "not effective." For treatment of breakthrough bleeding, IXINITY was rated as effective in terms of time of bleed, time for resolution of pain associated with bleed, or time for resolution of swelling. Subjects rated efficacy for treatment of bleeding as excellent in 51% and good in 32% of episodes. Treatment of breakthrough bleeding required a mean of 1.9 ± 2.2 infusions per episode.
- For on-demand subjects, the mean annualized bleeding rate was 16.14 ± 11.83 (median 16.4). All treatments, except for one, 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 on demand 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.
- IXINITY is effective for its claimed indications.

Safety Conclusions:

Comparability testing using laboratory and nonclinical evaluations showed that the current product was less immunogenic and similar biochemically to the original product. Therefore, immunogenicity and limited safety testing for the current product were provided, and general safety information was extrapolated to the current product from the legacy product. For former-IXINITY, the most important potential safety issue was development of immunogenicity to CHO host cell proteins in 20 of 68 subjects (29%) in the Treatment Phase, which resulted in the program for former-IXINITY being placed on clinical hold. No adverse reactions related to the anti-CHOP antibodies have been observed in these subjects. That product will no longer be used and will not be marketed. No subject who has received the current version of the product has developed new or rising anti-CHOP antibody titers.

- There were no deaths or related serious adverse reactions identified. Related adverse reactions to former-IXINITY were identified in 7 of 77 subjects (9%), with 15 adverse reactions of mild or moderate severity. The most common adverse 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. There were no cases of anaphylaxis, nephrotic syndrome, or severe hypersensitivity reactions. The safety profile at 50 and 100 exposure days is similar to the general safety profile.

- No subject developed inhibitory antibodies to FIX. Noninhibitory, non-neutralizing antibodies were found in 23 subjects [30%]. Dosing remained stable and no adverse reactions were related. Noninhibitory antibodies have developed in response to other products and the significance of these antibodies remains unknown.
- IXINITY is reasonably safe for use in its target population for its intended indications.

6.2 Clinical Trial #2: IB1001-02

Protocol IB1001-02 was titled *Study of Recombinant Factor IX Product, IB1001, in Previously Treated Pediatric Subjects with Hemophilia B.* The purpose of presenting this ongoing trial is as a framework for examination of the immunogenicity and limited safety data. Because the clinical trial is ongoing and was never intended as a pivotal trial for IXINITY, the data available and analyzed is only that relevant to the current licensing application. Information below is provided primarily when it is different than IB1001-01. Protocol Amendment 5 was submitted as part of the complete response to clinical hold, and was different than the previous protocol versions.

6.2.1 Objectives (Primary, Secondary)

The primary objectives are to evaluate the pharmacokinetics, safety, and efficacy in previously treated pediatric subjects with hemophilia B. Secondary objectives are to evaluate tolerance and compliance, and to evaluate safety during a treatment course of 50 exposure days.

6.2.2 Design Overview

The original trial design was as a non-randomized, open-label study. As of Amendment 5, the PK and Treatment Phases were terminated. Enrolled subjects who were in the Continuation Phase at the time of the amendment were invited to transition to modified-IXINITY and continue in Continuation phase for ≥ 12 months. Subjects could choose to stay until 2015-07.

- PK Phase: As of Amendment 5, there will be no further PK Phase enrollment. The PK Phase was to perform a modified, limited PK collection with a minimum of blood draws. PK Phase was to be performed > 28 days after screening, to spread out the draws over different 28-day periods.
- Treatment Phase: As of Amendment 5, there will be no further Treatment Phase enrollment. Treatment phase had the goal of gathering data from 50 exposure days. Treatment could be routien or on demand.
- Continuation Phase: Subjects after completion of Treatment Phase may continue into the Continuation Phase.
- Surgery Substudy: Subjects are allowed to enter a Surgery Substudy similar to IB1001-01. No subjects have enrolled in Surgery Substudy to date.
- Modified Phase (Continuation Phase with modified-IXINITY): Subjects will perform a recovery study after ≥ 4 days washout, prior to first infusion with modified-IXINITY.

6.2.3 Population

The population is a pediatric population ≤ 12 years old, previously treated for > 50 exposure days. As of Protocol Amendment 5, no new subjects will be enrolled in the trial. Inclusion criteria were similar to IB1001-01 Amendment 11, with the following differences:

- Need consent from parent or legal guardian
- Previous exposure of ≥ 50 exposure days (vs. 150 days in IB1001-01)
- Annualized bleeding rate of 0.33 bleeds per year (vs. 0.5 in IB1001-01), or in children < 5 years old occurrence of any one joint bleed at any time in their life

Exclusion criteria were similar to IB1001-01 Amendment 11.

6.2.4 Study Treatments or Agents Mandated by the Protocol

- Subjects who were in Continuation Phase, and on former-IXINITY outside the U.S. or marketed product, could transition to Modified Phase (Continuation Phase on modified-IXINITY) for ≥ 12 months.
- Dose for routine treatment in Modified Phase will be based upon the recovery study.
- Dose for on-demand treatment will be determined by investigator for seriousness of injury and bleeding episode.

6.2.6 Sites and Centers

As of Protocol Amendment 5, sites are located in India and the U.K. There are no U.S. sites at present. [Source #19, p. 28]

6.2.7 Surveillance/Monitoring

- PK Phase (Planned): After ≥ 4 day washout, a preinfusion sample will be collected for FIX and inhibitors. Then, a single intravenous dose of 75 IU per kg will be administered intravenously. Blood samples will be taken at 15-30 minutes and hours 4-6, 24-26, and 68-72.
- Modified Phase:
    - Recovery study will be done with FIX samples obtained before infusion and 5-15 minutes after infusion. Safety and efficacy assessments will be performed after 25 exposure days (ED) and every 3 months thereafter. Subject diary will be kept and reviewed after ED 5, 10-15, and 35.
    - Immunogenicity testing for antibodies against FIX and CHOP will be performed after ED 5, 10-15, 25, 35, 50, and every 3 months thereafter. After 12 months of Continuation Phase, testing will be every 6 months.

6.2.8 Endpoints and Criteria for Study Success

- PK Phase: Samples will be analyzed for incremental recovery, C(max), AUC, half-life, and clearance.
- Treatment and Continuation Phases: Efficacy endpoints include those from Trial IB1001-01 plus (a) cause and site of bleeding, (b) time from onset of bleeding to first infusion, (c) dose of product infused, and (d) FIX consumption.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Planned sample size was ≤ 22 subjects enrolled to obtain 20 evaluable subjects. Age distributions planned were ≤ 11 subjects < 6 years old and ≤ 11 subjects 6-12 years old. Now that no new subjects will be enrolled, it is not clear what will happen to the sample size.

6.2.10 Study Population and Disposition

Trial is ongoing. Nine subjects have been enrolled at last report.

6.2.10.1 Populations Enrolled/Analyzed

Trial is ongoing. Analysis will be submitted with final study report. The most recent data are from 2015-01-28. Study IB1001-02 enrolled nine pediatric subjects between 2011-05 and 2012-05. This includes two pediatric subjects who were included in the immunogenicity risk assessment dated 2014-Jan in e0019 and completed their study participation, as well as seven who have transitioned to modified-IXINITY between 2013-011 and 2014-03. Ages of the nine children at first infusion of former-IXINITY included three aged < 6 (aged 2, 4, 4) and six between 6 and < 12, inclusive (aged 7, 9, 10, 10, 11, 11). Ages of the seven children at first infusion of modified-IXINITY included all seven between 6 and 14, inclusive (6, 7, 9, 12, 12, 13, 14).

6.2.10.1.1 Demographics

Trial is ongoing. Analysis will be submitted with final study report. The seven boys exposed to modified-IXINITY had the following demographics: Races were Asian (n=6) and Caucasian (n=1), all male (n=7), aged 6-14 years. [Source #33, p.85]

6.2.11 Efficacy Analyses

Trial is ongoing. Analysis will be submitted with final study report.

6.2.11.1 Analyses of Primary Endpoint(s)

No formal statistical hypothesis testing is planned. Descriptive comparison will be performed using median rates and corresponding 95% confidence intervals.

Recovery PK data were gathered in Modified Phase in the pediatric trial. Levels were available at entry with pre-modification IXINITY (n=9 subjects, 15-30 minutes post infusion) and at transition (n=7 subjects, 5-15 minutes post infusion). In four cases where the levels could be compared, the levels were close. Missing data hampers the interpretation (Table 9). [Source #01, pp. 12, 52; Source #33, pp. 6-9]

Table 15: IXINITY PK and Initial Recovery in Study IB1001-02

Subject ID	Former-IXINITY	Modified-IXINITY
	PK Recovery (% factor IX activity)	Initial Recovery (% factor IX activity)
Subject 1	57	53
Subject 2	63	122 [likely an error]
Subject 3	40	43
Subject 4	58	66
Subject 5	N/A	50
Subject 6	64	N/A
Subject 7	22	N/A

[Source #33, p. 9]

6.2.11.2 Analyses of Secondary Endpoints

No formal statistical hypothesis testing is planned. Descriptive comparison will be performed using median rates and corresponding 95% confidence intervals.

6.2.11.3 Subpopulation Analyses

The population is divided into Ages < 6 years old and 6-12 years. No other subpopulation analysis is planned.

6.2.12 Safety Analyses

6.2.12.1 Methods

Data were analyzed descriptively. Tables of adverse events, and measures of immunogenicity were reviewed at multiple time points during the review of the submission.

6.2.12.2 Overview of Adverse Events

Trial is ongoing. Analysis will be submitted with final study report. The primary reason for including ongoing pediatric Trial IB1001-02 was to evaluate the adverse events of special interest. These data were included in Memo Section 6.2.12.5.

Exposure

Exposure in Trial IB1001-02 was to both former- and modified-IXINITY in Treatment/Continuation Phase and Modified Phase. Subjects (n=9) received 1141 infusions of former-IXINITY for routine treatment, median exposure was 110 ED (range 37-257 ED), mean dosing interval was 4.5 days (SD ±4.7 days, median 4 days, range 0-99 days [99 days may be an error]), mean dose was 1,200.2 IU/ED (SD ±362.68 IU/ED), and mean cumulative dose per subject was 149,507.7 IU (SD ±82,032.08 IU).

Subjects (n=7) received 370 infusions of modified-IXINITY for routine treatment, median exposure was 50 ED (range 26-99 ED), mean dosing interval was 3.7 days (SD ±1.1 days, median 4 days, range 0-8 days), mean dose was 1,557.7 IU/ED (SD ±582.01 IU/ED), and mean cumulative dose per subject was 81,860 IU (SD ±46,533.08 IU).

6.2.12.3 Deaths

There have been no deaths in IB1001-02.

6.2.12.4 Nonfatal Serious Adverse Events

No related serious adverse reactions have been reported, although the trial is ongoing.

6.2.12.5 Adverse Events of Special Interest (AESI)

- **Immunogenicity:** See Memo Section 6.1.12.5 for general discussion of immunogenicity.
    - *Anti-CHOP Antibodies (Anti-CHOP):*
        - Immunogenicity data from Trial IB1001-02 were available for 9 of 9 subjects, including [number] as of who transitioned from former- to modified-IXINITY. [Source #09, p. 7]

- Nine subjects in pediatric study IB1001-02 have been tested for anti-CHOP. Six subjects have been negative and three have tested positive for anti-CHOP. No subjects had anti-CHOP tested at screening since those screening dates preceded immunogenicity testing. Details from the three positive cases are given below. [Source #09, p. 16]
    - Subject (b) (6) had positive titer of 25,072 at first measurement after over 2 years of former-IXINITY. After transition to modified-IXINITY, titers decreased to 6,037. The only AE was an unrelated single episode of epistaxis 1 week after transition.
    - Subject (b) (6) had positive titer of 18,385 at first measurement after over 2 years of former-IXINITY. After transition to modified-IXINITY, titers decreased to 2,938. The only AE was one unrelated episode of extremity swelling prior to transition. There were no AE after transition.
    - Subject (b) (6) had positive titer of 1,968 at first measurement after over 2 years of former-IXINITY. After transition to modified-IXINITY, titers decreased to 353. He has suffered some moderate traumatic fractures, but no related AEs. [Source #09, p. 17]

o *Anti-FIX Antibodies:*

- No FIX inhibitors (neutralizing antibodies) have been identified in any subject.
- In Trial IB1001-02, with nine subjects on routine treatment for over 6 months, three of nine subjects (33%) were transiently positive for non-inhibitory anti-FIX antibody while on former- IXINITY prior to transition. Two had a single positive result followed by negative results, and one subject had three positive results followed by three negative results. After transition to modified-IXINITY, all seven transitioned pediatric subjects in the ongoing pediatric study were consistently negative for anti-FIX antibodies. No patterns of adverse reactions related to the non-inhibitory anti-FIX antibodies have been identified in any of the subjects.. [Source #09, Section 4.2.2, p. 27]
    - Two of these subjects with noninhibitory antibodies against FIX ((b) (6)) showed single positive results followed by negative results; one (b) (6)) showed three positive results followed by negative results.

6.2.12.6 Clinical Test Results

Trial is ongoing. Analysis will be submitted with final study report.

6.2.12.7 Dropouts and/or Discontinuations

Trial is ongoing. Analysis will be submitted with final study report.

6.2.13 Study Summary and Conclusions

Trial is ongoing. Analysis will be submitted with final study report. There is currently no evidence for incident development of antibodies against CHOP with administration of modified-IXINITY, which is consistent with decreased anti-CHOP immunogenicity. No FIX inhibitors have been identified. Pediatric subjects in IB1001-02 develop noninhibitory antibodies against FIX at approximately the same rate as subjects ≥ 12 years old in IB1001-01 (~ 30-33%). There is no known clinical significance to these antibodies. At this interval, the product appears acceptably safe but the trial will need to complete. The safety information can be used to support the pivotal trial for this application.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Safety data was assessed descriptively. No formal statistical analysis was performed in the assessment of safety. IB1001-01 was the pivotal trial; IB1001-02 was not intended as a pivotal trial for the application and was not included in the Table of Clinical Trials. However, because of the immunogenicity issues that arose early and the desire to view the totality of relevant information, immunogenicity and limited safety data from IB1001-02 was used in a supportive role.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The safety database includes data from use of original and modified-IXINITY in pivotal Clinical Trial IB1001-01 and ongoing pediatric Clinical Trial IB1001-02.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

[Pending response to information request sent 2015-02-24.]

8.2.3 Categorization of Adverse Events

The only issue with categorization of an adverse reaction occurred when the applicant allowed one local investigator to categorize development of noninhibitory anti-FIX antibodies as an adverse reaction while other sites did not characterize them as adverse events, even though there was no relevant difference or impact upon the subject. Ideally the applicant would have overruled the local investigator. We will make the appropriate changes in the label. Otherwise, no issues arose with categorization of adverse events or reactions. Because all studies were similar, using similar protocols, strong congruence would be expected.

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

No caveats are introduced by pooling the data across these two trials. Because all studies were similar, using similar protocols, no problems would be anticipated or occurred.

8.4 Safety Results

8.4.1 Deaths

No deaths occurred in any subject, in any trial, with any version of product, at any time.

8.4.2 Nonfatal Serious Adverse Events

No drug-related adverse reactions occurred in any subject, in any trial, with any version of product, at any time.

8.4.3 Study Dropouts/Discontinuations

Many subjects dropped out of the studies as a result of regulatory actions after discovery of anti-CHOP immunogenicity. No subjects discontinued because of adverse reactions. One subject withdrew because of perceived lack of efficacy, but there were mitigating factors.

8.4.4 Common Adverse Events

Common adverse events were as expected from the class of products. No new patterns of adverse events or safety signals were identified in any trial, with any version of product, at any time.

8.4.5 Clinical Test Results

With the exception of immunogenicity discussed in Memo Section 8.4.8, no patterns of clinical test result abnormalities were detected, or rose to the level of a safety signal, in any trial, with any version of product, at any time.

8.4.6 Systemic Adverse Events

No anaphylaxis, nephrotic syndrome, or severe hypersensitivity reactions occurred in any subject, in any trial, with any version of product, at any time.

8.4.8 Adverse Events of Special Interest

See Memo Section 8.5.8 for discussion of immunogenicity. No thromboembolic events occurred in any subject, in any trial, with any version of product, at any time.

8.5.8 Immunogenicity (Safety)

The legacy product that was responsible for development of anti-CHOP immunogenicity is no longer manufactured. No subject who received modified-IXINITY has developed incident anti-CHOP antibody titers or shown substantially increased titers. Rather, anti-CHOP titers have trended downwards in subjects who remained in the study and transitioned to marketed products or to modified-IXINITY. It is noted that some of the most recent titer measurements are made with the new version of the (b)(4) assay, so direct quantitative comparisons with the older (b)(4) are problematic. No related adverse events have been identified after years of exposure to IXINITY products.

No inhibitors have been identified in any subject at any time. Noninhibitory, non-neutralizing antibodies were found in approximately 30-33% of subjects. Dosing remained stable and no adverse reactions were related. Noninhibitory antibodies have developed in response to other products and the significance of these antibodies remains unknown.

8.6 Safety Conclusions

IXINITY was shown to be acceptably safe for use in the target population, for the claimed indications, at the labeled doses.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

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: Request for pediatric waiver and request for pediatric deferral were submitted.
- 2013-07: FDA published draft guidance on pediatric study plans.
- 2013: FDA agrees that submission of an iPSP is not required [Source #28].
- 2014-06-18: Presentation before the PeRC.

- 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. [Source #26]
  - 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 assessments. 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 [Source #29, p.68]. Three subjects were < 12 years old [Source #13, 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. See Memo Section 6.2.
- 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. [Source #30; 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. [Source #30]

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

Table 16. • Pediatric Timelines and Other Pediatric Data

Study	IB1001-01	IB1001-02	IB1001-04
Age Range	Current indication claim and ongoing Continuation Phase ≥ 12 years old	< 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 IXINITY
Number of Subjects	≥ 50 overall (adult and pediatric) evaluable on routine, ≥ 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

10. CONCLUSIONS

- The manufacturing process for modified rFIX now includes (b)(4) to remove host cell protein contaminants. The current version of modified-IXINITY was found to be acceptably safe and effective in subjects ≥ 12 years old with hemophilia B for on-demand treatment and for perioperative management.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.2 Risk-Benefit Summary and Assessment

- The current product has been shown to be comparable to product before modification, so efficacy was extrapolated to the current version of IXINITY from former-IXINITY. The efficacy profile was acceptable for on-demand bleeding and for perioperative management. Prophylaxis indication was blocked by exclusivity of another product.
- Because of comparability between versions of product and lack of evidence that indicated any meaningful clinical differences, general safety data were extrapolated to the current version of IXINITY from former-IXINITY. Immunogenicity and limited safety data were collected after subjects transitioned to the current version of product (see next paragraph). There were no deaths and no related serious adverse reactions. No FIX inhibitors were found in any subject at any time. Noninhibitory antibodies against FIX were found in approximately 30% of subjects in Trials IB1001-01 and IB1001-02, with no clinical consequences.
- The main safety issue in the legacy version of IXINITY was the anti-CHOP antibodies that led to clinical hold. These had no clinical ramifications, and the rest of the safety profile was acceptable. A (b)(4) step was added to the manufacturing process, to reduce potential immunogenicity. Comparability testing indicated that modified-IXINITY was physiochemically and biologically similar to former-IXINITY. Similarities were demonstrated in areas of potency, identity, purity/(b)(4) , and impurities. Animal testing showed substantially decreased immunogenicity. No subject who received current IXINITY has developed incident anti-CHOP reactivity. Subjects negative for anti-CHOP have remained negative. Most subjects who were positive for anti-CHOP had titers that decreased. Therefore, anti-CHOP immunogenicity is no longer considered a consequence of modified-IXINITY.
- The benefit-risk ratio for IXINITY is positive. No substantial issues remain.

11.4 Recommendations on Regulatory Actions

- From the clinical perspective, the clinical review team recommends approval.

11.5 Labeling Review and Recommendations

- Labeling review is complete. The final submitted label is acceptable. Extensive internal discussion occurred regarding language in several sections, but those discussions are completed and management has concurred on the language chosen.

11.6 Recommendations on Postmarketing Actions

- Pediatric assessment is currently deferred. Approval letter will include postmarketing commitment to complete the deferred study.

12. SOURCES

[Sources with links to internal sources removed].