Application Type	Original Application
STN	125426/0
CBER Received Date	04/06/2012
PDUFA Goal Date	02/04/2012
Division / Office	DH /OBRR
Priority Review	No
Reviewer Name(s)	Irwin M. Feuerstein, MD, MS Stephanie O. Omokaro, MD
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Inspiration Biopharmaceuticals, Inc.
Established Name	Recombinant Human Factor IX, IB1001
(Proposed) Trade Name	IXinity
Pharmacologic Class	Coagulation factor
Formulation(s), including Adjuvants, etc	Intravenous injection
Dosage Form(s) and Route(s) of Administration	1) Powder and solvent for injection, intravenous 2) Powder for solvent for injection, intravenous
Dosing Regimen	500, 1000, 1500 IU/vial
Indication(s) and Intended Population(s)	Control and prevention of bleeding episodes and perioperative management in adult and pediatric patients with hemophilia B

TABLE OF CONTENTS

Glossary

BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
CHO	Chinese hamster ovary
CHOP	CHO protein
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
DIS	Division of Inspections and Surveillance
eCTD	electronic Common Technical Document
FDAAA	Food and Drug Administration Amendments Act of 2007
GRMP	good review management practice
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ISE	integrated summary of efficacy
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NME	new molecular entity
OSE	Office of Surveillance and Epidemiology
PD	pharmacodynamics
PI	package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy

Page numbers: All page numbers in this document refer to the electronic page number from the digital documents as numbered by Adobe Acrobat.

1. Executive Summary

The product (IB1001/Ixinity) is a recombinant human factor IX manufactured in Chinese hamster ovary (CHO) cells. IB1001 is a lyophilized recombinant factor IX intended for intravenous administration as a replacement therapy or prophylaxis for patients with hemophilia B, including control and prevention of bleeding episodes and peri-operative management of hemophilia B patients undergoing surgery.

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

A total of 77 subjects were enrolled in one or more study phases and 68 of these subjects were used for analysis of safety and efficacy in the treatment phase. Overall, IB1001 was reported to be effective in preventing bleeding in hemophilia B subjects with a twice weekly prophylactic dose. The majority of subjects were dosed with 45-60 IU/kg twice weekly with a median annualized bleeding rate of 1.49 in the prophylaxis arm (N=60) and 11.51 in the on-demand arm (N=10).

Although formation of FIX inhibitors was not observed, non-neutralizing antibodies were seen in three subjects and development of anti-CHO antibodies was seen in 18 subjects. In order to further evaluate the clinical significance of these antibodies and to conduct a root cause anlaysis of this finding, the ongoing extension phase of the study including pediatric study was placed on clinical hold.

There are significant CMC issues that have been the subject of multiple teleconferences and amendments to discuss removal of the host cell impurities from the product.

Recommendation:
A complete response letter is recommended due to the presence of host cell impurities that led to anti-CHO antibody formation in subjects at a higher rate than observed with similar products manufactured using CHO cells.

Letter-Ready Comments:

1. Please submit the data on recipient antibodies against factor IX in a SAS transport file (.xpt).
2. Please modify the ACHOBAT file including revision of the patient identification field and presentation of titer values in a proper numerical and tabular format.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia B (Christmas disease) is a rare hereditary blood disorder caused by deficiency or dysfunction of factor IX resulting in bleeding secondary to abnormal clot formation. The hemophilia B gene is located on the X chromosome with an X-linked recessive inheritance pattern, affecting 1 in 100,000 male births and rare females.

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

Treatments for hemophilia B require replacement with a form of factor IX. Factor IX treatments include human plasma products such as fresh-frozen plasma or prothrombin complex concentrates. Monoclonally purified, recombinant factor IX preparations are now available and are the mainstay of therapy.

2.3 Safety and Efficacy of Pharmacologically Related Products

The only FDA-approved recombinant factor IX product is BeneFIX, which was approved in 1997. There are two plasma derived Factor IX products approved: Alphanine and Mononine.

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.

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

3.1 Chemistry, Manufacturing, and Controls

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

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

4.1 BLA/IND Documents that Serve as the Basis for the Clinical Review

Documents pertinent to the review of this submission were provided in this BLA 125426 as well as IND 13551.

4.2 Table of Studies/Clinical Trials

Three trials were submitted as part of the application. The three trials and four phases are summarized in Table 1 below.

Table 1: IB1001 Clinical Development

Study No.	Study Purpose and Design	Patient Population	Study status	Countries
IB1001-01 (PK phase)*	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-∞) 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	USA, UK ,Italy, Israel,
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)	20 subjects for 50 ED - completed	USA, UK, Italy Israel
			50 subjects for 50 ED -completed	USA, UK, Italy, France, Poland, Israel, India
IB1001-01 (Continuation phase)	Long term safety and efficacy of IB1001; up to 100 ED	Same as above (see PK Phase)	50 subjects for 100 ED – post approval commitment; ongoing	USA, UK, Italy, France, Poland, Israel, India
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 16 procedures in 14 subjects	USA, Israel, Italy, UK, India, France
IB1001-02	PK, safety and efficacy in previously treated children 0-12 years of age for at least 50 exposure days	Immunocompetent children 0-12 years of age with severe hemophilia B and a history of frequent bleeding episodes, with at least 50 prior exposure days, adequate organ function, signed informed consent by parent or guardian.	ongoing; post-approval commitment	USA, UK, Poland, India, Turkey, Mexico
IB1001-03	Safety and efficacy in previously untreated children <6 years of age (treatment for up to 3 years or 100 ED)	Children < 6 years with severe hemophilia B and no prior therapy for hemophilia, adequate organ function, signed informed consent by parent or guardian.	not yet initiated; post-approval commitment	to be determined

* Regulatory requirements for number of subjects in PK and treatment phases differ between FDA and EMA. Study IB1001-01 was designed to address both sets of requirements.

[Source: Page, 11, Clinical Overview, BLA 125426/0]

4.3 Consultations

No consultations were requested by the clinical team.

4.4 Advisory Committee Meeting (if applicable)

N/A

4.5 External Consults/Collaborations

N/A

5. Applicable Literature

European Medicines Agency. (2011, July 21). Guideline on clinical investigation of recombinant and human plasma-derived factor IX products (EMA/CHMP/BPWP/144552/2009). Retrieved from http://www.ema.europa.eu

Ingerslev, J., Christiansen, K., Ravn, H. B., Bray, G. L., & Gomperts, E. D. (2002). Antibodies to heterologous proteins in hemophilia A subjects receiving recombinant factor VIII (Recombinate). *Thromb Haemost 87*, 626-634.

Xue, L., Johnson, R., & Gorovits, B. (2010). Prevalence and isotypic complexity of the anti-chinese hamster ovary host cell protein antibodies in normal human serum. *The AAPS Journal, 12*(1), 98-106.

Okada, M. & Hitsumoto, Y. (2006). A unique monoclonal antibody against human plasma fibronectin, which recognizes an epitope on the surface of a subpopulation of polymorphonuclear neutrophils. Hybridoma.(Larchmt.), 25, 202-208. 10.1089/hyb.2006.25.202

Zanetti, M. & Takami, T. (1984). Mesangial immune deposits induced in rats by antibodies to fibronectin. Clin Immunol Immunopathol., 31, 353-363.

Dixit, V. M., Haverstick, D. M., O'Rourke, K., Hennessy, S. W., Broekelmann, T. J., McDonald, J. A. et al. (1985). Inhibition of platelet aggregation by a monoclonal antibody against human fibronectin. Proc.Natl.Acad Sci U.S A, 82, 3844-3848.

Kempfer, A. C., Farias, C. E., Carballo, G. A., Silaf, M. R., & Lazzari, M. A. (1999). The effect of polyclonal antibody against fibronectin on von Willebrand Factor multimeric size. Thromb.Res, 96, 161-167. S0049-3848(99)00098-5

Flock, J. I. & Brennan, F. (1999). Antibodies that block adherence of to fibronectin. Trends Microbiol., 7, 140-141. S0966842X99014833

Girard, D., Raymond, Y., Labbe, P., & Senecal, J. L. (1995). Characterization of a novel human antibody xenoreactive with fibronectin. Clin Immunol Immunopathol., 77, 149-161. S0090122985711385

Atta, M. S., Powell, R. J., & Todd, I. (1994). The influence of anti-fibronectin antibodies on interactions involving extracellular matrix components and cells: a possible pathogenic mechanism. Clin Exp.Immunol, 96, 26-30.

Atta, M. S., Powell, R. J., Hopkinson, N. D., & Todd, I. (1994). Human anti-fibronectin antibodies in systemic lupus erythematosus: occurrence and antigenic specificity. Clin Exp.Immunol, 96, 20-25.

Underwood, P. A., Dalton, B. A., Steele, J. G., Bennett, F. A., & Strike, P. (1992). Anti-fibronectin antibodies that modify heparin binding and cell adhesion: evidence for a new cell binding site in the heparin binding region. J Cell Sci, 102 (Pt 4), 833-845.

Stefanato, C. M., Gorkiewicz-Petkow, A., Jarzabek-Chorzelska, M., Jablonska, S., & Chorzelski, T. (1992). Morphea with high titer of fibronectin antibodies. Int J Dermatol., 31, 190-192.

Howard, J. & Pilkington, G. J. (1990). Antibodies to fibronectin bind to plaques and other structures in Alzheimer's disease and control brain. Neurosci.Lett., 118, 71-76. 0304-3940(90)90251-4

Chernousov, M. A., Faerman, A. I., Frid, M. G., Printseva, O. Y., & Koteliansky, V. E. (1987). Monoclonal antibody to fibronectin which inhibits extracellular matrix assembly. FEBS Lett., 217, 124-128.

Klein, C. L., Angaswamy, N., Jason, W., Shenoy, S., & Mohanakumar, T. (2012). Transplant Glomerulopathy Is Associated with the Production of Auto-Antibodies Against Fibronectin and Collagen Type IV. American Journal of Transplantation, 12, 541-542.

Ebbinghaus, C., Scheuermann, J., Neri, D., & Elia, G. (2004). Diagnostic and therapeutic applications of recombinant antibodies: Targeting the extra-domain B of fibronectin, A marker of tumor angiogenesis. Current Pharmaceutical Design, 10, 1537-1549.

6. Discussion of Individual Studies/Clinical Trials

The study was comprised of four components: pharmacokinetic, treatment safety and efficacy (prophylaxis, on demand), surgery, continuation, as shown in Figure 1 below.

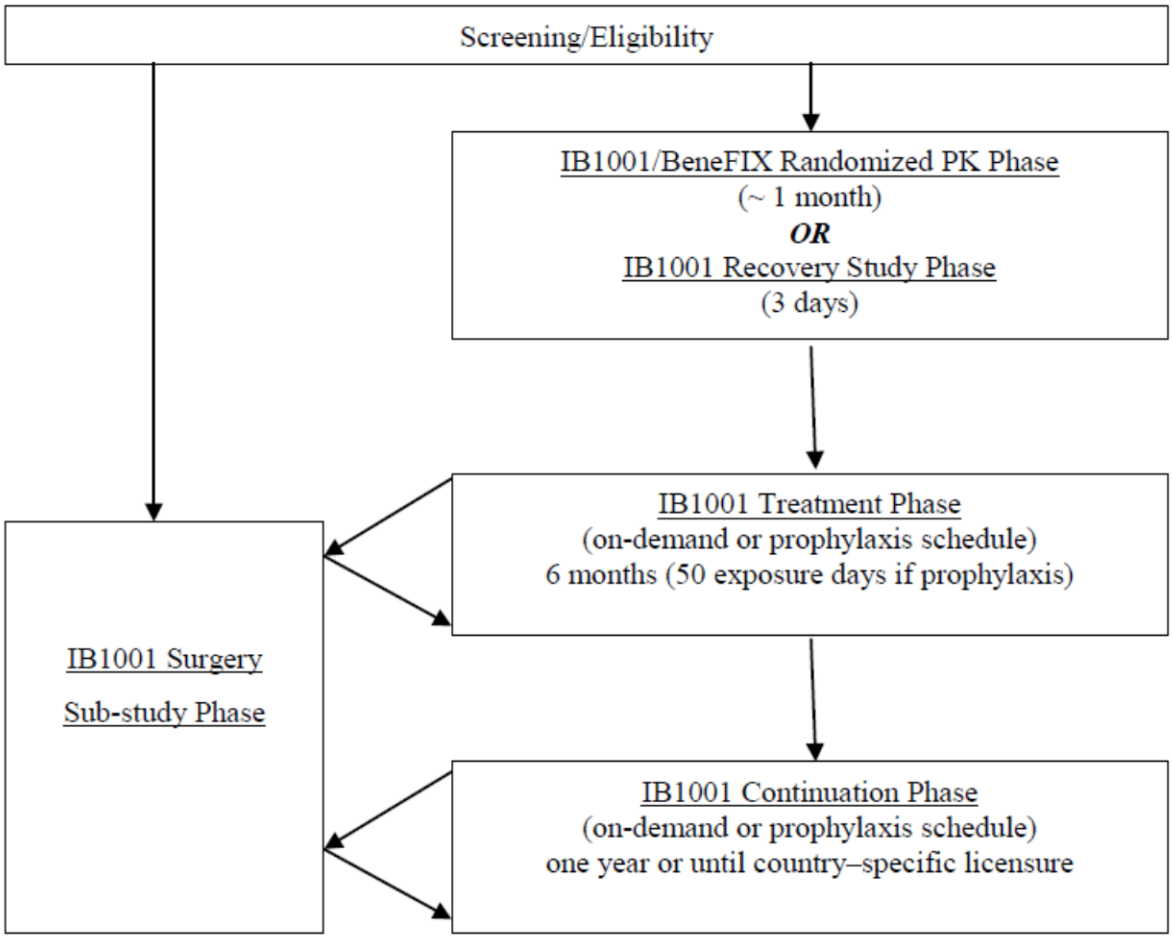


Figure 1: Overview of Study IB1001-01

[Source: BLA 125426/0]

6.1 Trial #1

Pharmacokinetic Study, IB1001, in Subjects with Hemophilia B

No safety issues were identified in this study.

The pharmacokinetic (PK) results are covered in the review conducted by clinical pharmacology.

6.1.1 Objectives (Primary, Secondary, etc)

To evaluate the pharmacokinetic parameters for IB1001 in previously treated subjects with hemophilia B, compare them with a licensed comparator product, and gather initial human safety data

6.1.2 Design Overview

The study is a dual arm, sequential, randomized, crossover study, phase 1 trial. Single doses of IB1001 or BeneFIX were given in randomized order to subjects, separated by at least five days of washout and up to a maximum of 28 days. A washout period for any prior factor IX product of at least five days was done before evaluation and the first infusion. Identical single intravenous doses of 75 ± 5 U/kg were administered.

Factor IX levels and evidence for prior inhibitor development were gathered prior to infusion. Clinical and laboratory safety assessment were done after infusion. These included thrombogenic markers (D-dimer, F1+2, and TAT) that were evaluated pre-infusion and at multiple times post infusion.

6.1.3 Population

Requirements for this study included severe (factor IX activity ≤2 U/dL) deficiency with a minimum of 3 bleeding episodes over the preceding 6 months or 6 bleeding episodes over the preceding 12 months while on on-demand therapy. Subjects also had at least 150 prior exposure days with a factor IX product.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Single 75 U/kg intravenous doses of IB1001 and BeneFIX were administered and evaluated sequentially. No other products were specified by the protocol.

6.1.5 Directions for Use

A single intravenous dose of factor IX product was given for each arm. An unblinded pharmacist or infusionist gave the drug. Other study personnel were blinded. No other special instructions were used.

6.1.6 Sites and Centers

The trial was a multi-investigator, multicenter, international study. Sites from the U.S. were included.

6.1.7 Surveillance/Monitoring

The safety of this study was reviewed by an independent data and safety monitoring board (DSMB), who met at routine intervals between 3 and 12 months including February and September 2010. Screening assessments were provided in Table 5.1.1 in the protocol document. Physical examinations, medical histories, and concomitant

medications were assessed at the beginning of each time period. Adverse events and vital signs were recorded at each PK time point. The total duration for PK assessment was 72 hours, with evaluation of thrombogenicity during the first 24 hours,

The central laboratory, (b) (4) created a distribution of values for all three thrombogenic markers (D-dimer, TAT, and F1+2) based on negative human plasma controls. The cut point chosen was any value outside the 99% range for normal subjects.

6.1.8 Endpoints and Criteria for Study Success

The pharmacokinetic trial was conducted as a non-inferiority trial comparing IB1001 and BeneFIX. The pharmacokinetic analysis of measured and derived parameters, including area under the curve of concentration vs. time, was done by the clinical pharmacologists. Clinical safety was assessed using descriptive statistics. Other than PK, there is no efficacy component to this part of the trial.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The estimated sample size was 28 and 32 subjects were enrolled.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Inclusion criteria included:

1. Severe hemophilia B (factor IX activity ≤2 U/dL)
2. On demand therapy with a minimum of 3 bleeding episodes over the preceding 6 months or 6 bleeding episodes over the preceding 12 months; subjects on prophylaxis with a bleeding pattern as above demonstrated prior to starting prophylaxis
3. Previously treated subjects with a minimum of 150 exposure days to a factor IX preparation

Exclusion criteria included:

1. History of factor IX inhibitor ≥0.6 Bethesda units
2. Existence of another coagulation disorder

The overall population enrolled in the PK portion was 32 subjects. Since there were no dropouts, the analysis, safety, and intent-to-treat populations were identical.

6.1.10.1.1 Demographics

Average age was 32 years; age range was 15-64 years. All but two subjects were Caucasian. All were male.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The two arms had similar average baseline levels of factor IX. The study excluded subjects with significant concurrent illnesses and subjects receiving drugs such as chemotherapy, aspirin, or other anticoagulants.

6.1.10.1.3 Subject Disposition

Thirty two subjects were enrolled. All were randomized and completed both study periods. All received the 75 IU/kg dose for both arms.

6.1.11 Efficacy Analyses

Please refer to the clinical pharmacology memo. No clinical study of efficacy was performed as part of this segment of the trial.

6.1.11.1 Dropouts and/or Discontinuations

There were no dropouts or discontinuations.

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety of study subjects was monitored by history and physical examination, laboratory measurements that included markers of thrombogenicity and immunogenicity, and assessments of bleeding. The protocol included prespecified definitions of adverse reactions including severity, seriousness, and relatedness. A DSMB monitored the study.

Preinfusion levels of factor IX, inhibitory, and non-inhibitory antibodies were assessed. According to table 9.5-2 on page 30 of the BLA clinical study report, the antibody titers were assessed prior to the first dose. They were not repeated between doses or after the second dose. Routine laboratory tests were not assessed during the PK part of the study.

Safety assessments are presented in Tables 9.5-1 and 9.5-2 below.

Table 9.5-1: Schedule for Screening Visit Evaluations

Screening Visit	
Informed consent form	X
Inclusion/exclusion criteria:	X
Medical and hemophilia-related history	X
CD4	X
Diagnosis of another coagulation disorder or serious medical or social condition	X
History of compliance	X
Inhibitor titers	X
Concomitant medications[a]	X
Previous & current history of factor IX use	X
Demographics	X
Blood samples:	X
CBC with differential	X
High-sensitivity C-reactive protein (hs-CRP)	X
Blood chemistries[b]	X
Inhibitor titer	X
Non-inhibitory antibodies	X
a-CHO assay	X
Mutation typing (if necessary)	X
Urinalysis	X
Vital signs	X
Physical exam	X
Physical therapy assessment	X
Health status and quality of life (QoL)[c]	X
Instructions for diary completion	X
Patient training on IB1001 reconstitution and administration	X

[a] Concomitant medications taken within 14 days of screening were recorded.

[b] Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), blood urea nitrogen (BUN), uric acid, creatinine, total bilirubin, and glucose.

[c] Quality of life assessments were done at the beginning of the study visit, and assessed for subjects who are at least 12 years of age.

Table 9.5-2: Schedule for BeneFIX/IB1001 PK Study Phase

Part I:

BeneFIX/IB1001 PK Study

	Period 1 (Day 1-15)	Period 2 (5-28 days from Period 1 Infusion)
Vital signs	X	X
Physical exam	X	X
Adverse events	X	X
Medical history	X	X
Concomitant medications	X	X
75 ± 5 IU/kg dose of BeneFIX or IB1001	X	X
PK assessments[b]	X	X
Inhibitor titer	Xa	
Non-inhibitory antibodies	Xa	

[a] Inhibitor titer and non-inhibitory antibodies must have been measured within 15 days of start of BeneFIX/IB1001 PK Study.

[b] See BeneFIX/IB1001 PK Assessments table in Part II.

[Source: pp. 29-30, body.pdf, PK study, BLA 125426/0]

6.1.12.2 Overview of Adverse Events

The safety profile of IB1001 was compared side-by-side with BeneFIX. The safety profiles were very similar.. Eight adverse events were reported in each arm. Fewer subjects in the IB1001 arm (n=3, 9%) experienced adverse events than in the comparator arm (n=6, 19%). Adverse events in the IB1001 arm included back pain (n=1, 13%), headache (n=3, 38%), vomiting (n=1, 13%), diarrhea (n=1, 13%), fever (n=1, 13%), and viral infection (n=1, 13%). There was no evidence of thrombogenicity. Review of the submitted laboratory results did not reveal patterns of abnormalities to differentiate the products. Two occurrences of headache were considered related to treatment.

One adverse event was reported as severe. It was a case of grade 3 hemarthrosis in an ankle of subject (b) (6). Hemarthoses are a known complication of the underlying disease, and it is impossible to know from one case whether it is an adverse reaction, a lack of efficacy, or just a consequence of hemophilia.
[Source: p. 55, body.pdf, PK study, BLA 125426/0]

6.1.12.3 Deaths

There were no deaths in subjects who received IB1001.

6.1.12.4 Nonfatal Serious Adverse Events

Nonfatal serious adverse events were not reported for this phase of the protocol.

6.1.12.5 Adverse Events of Special Interest (AESI)

Events of special interest would include thromboses, hemolysis, transmitted infections, and immunogenicity. No episodes of thrombosis, hemolysis, transmitted infection, or immunogenicity were observed in the PK study.

6.1.12.6 Clinical Test Results

Abnormal values for thrombogenic assays were presented in Table 12.4-2. Review of this data did not reveal any pattern that differentiated IB1001 from BeneFIX. Subjects in both arms showed similar patterns of elevation of TAT, D-dimer, and F1+2. Interpretation was limited by very wide ranges of values even in the preinfusion measurements and especially in the D-dimer.

6.1.12.7 Dropouts and/or Discontinuations

None.

6.2 Trial #2

Safety and Efficacy of IB1001 in Subjects with Hemophilia B

6.2.1 Objectives (Primary, Secondary, etc)

The objective of this part of the trial was to evaluate the safety and efficacy of IB1001 in subjects with hemophilia B. Safety was assessed for acute infusion reactions and inhibitor formation, while efficacy was determined by breakthrough bleeding during prophylaxis and on-demand treatments.

6.2.2 Design Overview

The treatment phase of the trial was an open-label, non-randomized design intended to serve as the pivotal trial for licensure. Similar to the PK study, a minimum of 150 exposure days to a factor IX preparation was a study enrollment requirement.

The choice of prophylaxis or on-demand treatment was at the discretion of the investigator and subject. Subjects were allowed to switch treatment plans as desired. Spontaneous bleeding was treated with an additional infusion with option to repeat if needed. Assays for inhibitor and anti-CHO formation were done prior to initial infusion and at three-month intervals.

6.2.3 Population

The analysis in the study report was performed after at least 50 subjects had been treated for at least 50 exposure days. Additional subjects with fewer than 50 ED were included for completeness of the safety information.

6.2.4 Study Treatments or Agents Mandated by the Protocol

The planned prophylaxis regimen was an intravenous 50-75 IU/kg dose of IB1001 twice a week, anticipating at least 50 exposure days over six months. Changes in dose or infusion frequency could be made at the discretion of the investigator. Subjects in the on-demand arm were followed for at least six months after which annualized bleed rates were calculated.

6.2.5 Directions for Use

The anticipated intravenous doses for prophylaxis and on-demand regimens were 50-75 IU/kg and 50-100 IU/kg, respectively. No special directions were needed.

6.2.6 Sites and Centers

The trial was a multi-investigator, multicenter, international study, including sites different from the PK trial. Several U.S. sites were included.

6.2.7 Surveillance/Monitoring

Safety assessments for screening and ongoing treatment are given in Table 9.5-1 of the treatment study report. Safety monitoring included routine laboratory assessment, diary records, and quality of life metrics. Measurements of inhibitory and non-inhibitory antibodies to IB1001 as well as anti-CHO antibodies were assessed every three months. Thrombogenicity markers were not evaluated after the PK study.

6.2.8 Endpoints and Criteria for Study Success

Efficacy endpoints included control of spontaneous bleeding in the prophylaxis arm and treatment of hemorrhagic bleeding episodes in both prophylaxis and on-demand settings. Safety was determined by reporting of adverse events by subjects and investigators. Subjects recorded adverse events in their diaries and were questioned at the three-month evaluations.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Statistical plans for safety and efficacy were limited to descriptive statistics and examination by the reviewer. Annualized bleeding rates were calculated. Sample size calculations were presented in section 9.7.2. The planned sample size for the treatment study phase was up to 55 subjects on prophylaxis and up to 20 subjects using an on-demand schedule.

6.2.10. Results

6.2.10.1 Populations Enrolled/Analyzed

Inclusion criteria included:

1. Severe (factor IX activity ≤2 U/dL) hemophilia B subjects on-demand therapy with a minimum of 3 bleeding episodes over the preceding 6 months or 6 bleeding episodes over the preceding 12 months; subjects on prophylaxis with a bleeding pattern as above demonstrated prior to starting prophylaxis

Exclusion criteria included:

1. History of factor IX inhibitor ≥0.6 Bethesda units
2. Existence of another coagulation disorder
3. History of adverse reaction to either plasma-derived factor IX or recombinant factor IX that interfered with the subject's ability to treat bleeding episodes with a factor IX product

A total of 68 subjects were enrolled, including 59 subjects who enrolled in the prophylaxis arm, eight in the on-demand schedule, and one subject who was enrolled as 'targeted' prophylaxis. Secondary to his infrequent infusions, the 'targeted' subject is included in the on-demand group while on prophylaxis.

Treatment phase analyses included all subjects who received at least one dose of IB1001.

6.2.10.1.1 Demographics

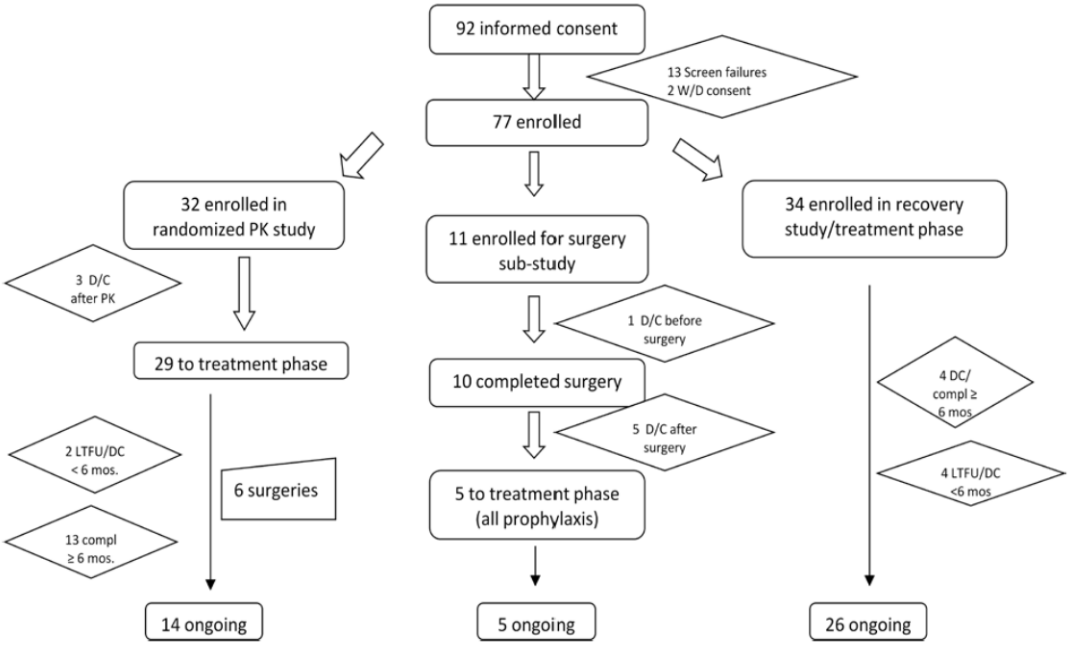
Overall average age was 30 years, with on-demand subjects being seven years older on average. Subjects were 79% Caucasian, including all those who selected an on-demand regimen.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The 60 subjects on a prophylaxis regimen achieved a mean compliance of 85%. Compliance ranged from 18% to 107%, the latter a result of a patient who received more infusions than expected.

6.2.10.1.3 Subject Disposition

Three subjects on an on-demand regimen switched to a prophylaxis regimen, thus they are included in both groups during the relevant time periods. One subject who switched from prophylaxis to on-demand after entering the treatment phase is also counted in each group during the relevant time period. The subject disposition chart from the BLA Clinical Study Report is presented below. A total of 77 subjects were enrolled in one or more study phases. Patients discontinued or lost to follow up are discussed in section 6.2.11.4.



6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

, IB1001 was effective in preventing bleeding in hemophilia B subjects. Seventy percent of subjects were dosed 45-60 IU/kg twice weekly with a median annualized bleeding rate of 1.49 in the prophylaxis arm (N=60) and 11.51 in the on-demand arm (N=10).

[See Table 11.4-7 from BLA Clinical Study Report]

Table 11.4-7: Summary of Annualized Bleed Rates

	Prophylaxis N=60	On Demand N=10
Annualized Bleed Rate		
n	60	10
Minimum	0.00	3.25
25th percentile	0.00	10.44
Median	1.49	11.51
75th percentile	3.62	15.25
Maximum	24.59	42.55
Mean	1.21	3.73
SD	1.24	1.28
95% CI	(0.89,1.53)	(2.81,4.64)
p-value		<0.0001

The efficacy analysis for treatment phase by regimen included N=63 for prophylaxis (59 enrolled but 4 switched from on-demand), and N=10 for on-demand (9 enrolled and 1 switched from prophylaxis).

Forty-one percent (N= 26 of 63) of subjects on prophylaxis reported no breakthrough bleeding episodes from months 3.8-33.5 whereas the remainder (59%) of subjects on prophylaxis had a total of 204 bleeding episodes with 59% related to trauma, 28% spontaneous and 13% of unknown cause. The 10 subjects on on-demand reported a total of 151 bleeding episodes with 21% related to trauma, 67% spontaneous and 12% of unknown cause. The median number of bleeding episodes for individuals on prophylaxis was 1.5 compared to a median number of 11.5 for subjects with an on-demand regimen. See adapted Table 11.4-1 from the BLA Clinical Study Report for a summary 4 of 18 subjects with an annual bleed rate >3. These subjects notably had increased bleeding rates after initiating IB1001 prophylaxis which was concerning. The worsening of bleeding frequency after prophylaxis in these subjects was attributed to poor compliance and trauma. This explanation was acceptable and supported by the review of clinical narratives for these 4 subjects. The remaining subjects had annual bleed rates between 0-3.

Table 11.4-1: Prophylaxis Subjects with Annualized Bleeding Rate >3

Subject ID	Annual Bleed Rate	# of Bleeds on Prophy	Months on Prophy	Prescribed regimen for prophy	Mean infusion dose*	Regimen change	Comments
(b) (6)	14.6	25	20.5	50 IU/kg 2x weekly	47-70 IU/kg	incr to 57 IU/kg to "escape ankle bleeding"	poor compliance and >50% bleeds due to trauma
	7.5	15	24.1	50 IU/kg once weekly	49-62 IU/kg	incr to 60 IU/kg due to once weekly dosing	infuses once weekly (as prescribed) and >50% bleeds due to trauma
	7.4	15	24.3	60 IU/kg 2x weekly	56-80 IU/kg	70 IU/kg due to bleeding; 52 IU/kg "better regimen"; 3x weekly due to bleeding; back to 62 IU/kg due to unsatisfactory response	inconsistent documentation and poor compliance; note first bleed was reported before start of prophylaxis
	3.8	7	22.3	27 IU/kg 2x weekly	24-40 IU/kg	29 IU/kg 3.5x weekly due to sub-optimal prophylaxis coverage	4 nosebleeds and one report of hematuria were not treated; one bleed due to moderately severe fall (AE)

For each bleeding episode, subjects were asked to rate the efficacy of IB1001 on a four point scale of excellent to poor. Due to implementation issues between the sponsor and CRO, 24% of the bleeding episodes were not rated for efficacy. Of those that were reported, 52.6% were rated as excellent, 29.5% as good, 12.2% as fair and 5.8% as poor. The majority of bleeding as well as associated pain and swelling were resolved within 24 hours with a mean of 1.7 infusions required to stop the bleed.

[See Table 11.4-2 from BLA Clinical Study Report]

Table 11.4-2: Subject Assessment of Efficacy of IB1001

	Prophylaxis N=60 n (%)	On Demand N=10 n (%)	Total N=65 n (%)
Number of Subjects with Bleeds	37	10	42
Number of Bleeds	209	151	360
Subject Rating of Efficacy			
Not Rated	53 (25.4)	32 (21.2)	85 (23.6)
Rated	156 (74.6)	119 (78.8)	275 (76.4)
Excellent	82 (52.6)	43 (36.1)	125 (45.5)
Good	46 (29.5)	65 (54.6)	111 (40.4)
Fair	19 (12.2)	8 (6.7)	27 (9.8)
Poor	9 (5.8)	3 (2.5)	12 (4.4)

Additionally, 73% of bleeding episodes were controlled with only one dose of IB1001.

[See Table 11.4-3 from BLA Clinical Study Report]

Table 11.4-3: Infusions Required for Treatment

Number of Infusions/bleed	Frequency	Percent of all Bleeds
1	249	72.59
2	52	15.16
3	13	3.79
4	9	2.62
5	7	2.04
6	3	0.87
7	2	0.58
8	3	0.87
9	1	0.29
11	1	0.29
19	1	0.29
20	1	0.29
24	1	0.29

The bleeding episodes for which 5 or more doses of IB1001 were given [Table 11.4-3 from BLA Clinical Study Report] were reported to be related to trauma (N=8), located in target joints (N=5) or muscles (N=4).

Investigators were asked to rate efficacy at each three month follow-up visits on a 4-point scale from effective to not applicable. Of the 235 subject visits 95% were rated as effective prevention and treatment of bleeding by IB1001, 3% partially effective, 1% were not applicable and 1% required further evaluation.

6.2.11.2 Analyses of Secondary Endpoints

None

6.2.11.3 Subpopulation Analyses

Data for pediatric subjects included 3 subjects <12 years of age and 8 subjects 12 - <18 years of age. The average adjusted recovery of IB1001 was lower in pediatric subjects with 0.83 in subjects 12-<18 years and 0.74 in subjects <12 years compared to 0.99 in adult subjects. Pediatric subjects were all assigned to prophylaxis regimens >50 IU/kg given once or twice weekly with annualized bleed rates $\leq$3.

6.2.11.4 Dropouts and/or Discontinuations

Of the 68 subjects in the treatment phase, 5 subjects withdrew or were lost to follow-up prior to completion of six months of treatment.

6.2.12 Safety Analyses

6.2.12.1 Methods

Details of the safety assessments were presented in Table 9.5-1 and shown below.

Table 9.5-1: Safety and Efficacy Assessments During Treatment and Continuation Study Phases IB1001-01

	Screening	Every 3 months during treatment/continuation	End of Study or Early Termination
Medical history	X	X	X
CBC with differential	X	X	X
Blood chemistries[1]	X	X	X
Inhibitor titer	X	X	X
Non-inhibitory antibodies	X	X	X
a-CHO assay	X	X	X
Mutation typing (if consented)	X		
Urinalysis	X	X	X
Vital signs	X	X	X
Physical exam	X	X	X
Physical therapy assessment	X	X	X
Health status and quality of life (QoL)	X	X	X
Subject diary		X	X
Infusions		X	X
Bleeding summary		X	X
Efficacy assessment[2]		X	X
Adverse event and con meds		X	X
Compliance		X	X
Recovery study (if terminated for lack of efficacy)			X

[1] Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), blood urea nitrogen (BUN), uric acid, creatinine, total bilirubin, and glucose.

[2] If, in the opinion of the investigator, efficacy response has been sub-optimal, a test for inhibitor and a recovery study (factor IX measurements at 15 minutes and 1 hour post-infusion) may be considered.

Safety of study subjects was monitored by history and physical examination, laboratory measurements, assays for development of immunogenicity, and assessments of bleeding. Longitudinal clinical laboratory and antibody assays are added above those performed in the PK study, while the tests for thrombogenicity were removed. Bleeding was monitored and considered an efficacy outcome. However, subjects were monitored for development of inhibitors that might predispose to bleeding. The protocol included prespecified definitions of adverse reactions including severity, seriousness, and relatedness. A DSMB monitored the study.

6.2.12.2 Overview of Adverse Events

Overall, there were 258 adverse events including 228 events in 46 subjects (72%) from the prophylaxis regimen and 30 events in 7 subjects (70%) on-demand. There were no cases of nephrotic syndrome, inhibitors, anaphylaxis, or deaths. Rare adverse events included asthma, rash, cough, and chest pain.

There were no patterns suggestive of continuing increased consumption or patterns suggestive of inhibitor formation. Formation of antibodies against CHO proteins is discussed in section 6.2.12.5.

Number and percentage of adverse events by treatment group are presented in Table 7 below.

Table 7: Number and Percentage of Adverse Events by Treatment During Treatment Study Phase

System Organ Class Preferred Term	Prophylaxis N=63 n (%)	On Demand N=10 n (%)	Total Treatment N=68 n (%)	Total Study N=77 n (%)
Number of AEs	228	30	258	263
Number of Subjects with AEs	46 (73.0)	7 (70.0)	51 (75.0)	52 (67.5)

6.2.12.3 Deaths

No deaths occurred in this population.

6.2.12.4 Nonfatal Serious Adverse Events

Seven SAEs were reported. Based upon the narratives provided, none appear to be related to IB-1001.

6.2.12.5 Common Adverse Events

Approximately 75% of subjects experienced at least one adverse event. Ten severe adverse events occurred in the study, including the 7 SAEs. Review of these cases indicates that the events are unrelated to IB1001. The most common adverse reaction was headache, with at least one headache reported in approximately 9% of all subjects. Less than 1% of individual infusions were associated with headache. Also common were dizziness, arthralgias, nasopharyngitis, fever, nausea, vomiting, and diarrhea.

6.2.12.6 Adverse Events of Special Interest (AESI)

Events of special interest included thromboses, hemolysis, transmitted infections, and immunogenicity.

Eighteen out of 68 subjects in the entire trial developed antibodies against CHO host cell proteins. Sixteen of the 18 subjects were in the treatment study. The other two subjects

were in the surgery study only. No clinically relevant abnormalities were reported in these subjects. A written request has been made for more quantitative and temporal details on the formation of anti-CHO antibodies. A response is pending for this information request.

No case of confirmed thrombosis or hemolysis was detected.

6.2.12.7 Clinical Test Results

Aside from the antibodies to CHO host cell proteins, there were no patterns of clinically significant laboratory abnormalities that could be ascribed to IB1001. Similarly, no patterns of abnormal vital signs or physical examination findings were noted.

Thirteen subjects displayed hypereosinophilia at some point during the trial. Eight subjects had increased eosinophils at screening. Of the eight, only two showed further increase by at most 2.2%. Five subjects with normal screening levels developed increased eosinophils during the trial. The most striking increase was in subject (b) (6) who increased from a level of 2% to 11% by month 9. This subject did not have antibodies to FIX or CHO at the conclusion of the study. The other subjects who developed eosinophilia had lesser increases and levels that varied up and down.

Of the 13 subjects who had eosinophilia, 2 had elevated eosinophil counts at screening and subsequently developed antibodies against CHO proteins. One of these 2 subjects had a screening eosinophil count of 17% which declined over time to 8-9%. The second subject had a screening eosinophil count of 8% which increased to 9% at 3 months. Thus, none of these instances showed a temporal pattern suggestive of a correlation between development of eosinophilia and anti-CHO antibody.

6.3 Trial #3

Name of trial: Safety and Efficacy of IB1001 in Subjects with Hemophilia B Undergoing Surgery

6.3.1 Objectives (Primary, Secondary, etc)

The objective of the surgery substudy was to evaluate the safety and efficacy of IB1001 in subjects with hemophilia B in the setting of major surgery. The primary objective is to assess the control of bleeding for major surgical procedures.

6.3.2 Design Overview

The surgery study was a non-randomized, open-label trial intended to serve as a pivotal trial for the surgical indication for IB1001. Subjects were allowed to participate in the surgery study only or could transfer between the treatment arms as desired. The surgery study was open for enrollment after the PK substudy demonstrated that it was safe to proceed.

6.3.3 Population

Many complications of hemophilia require surgical intervention including chronic destructive arthropathy or acute intracranial hemorrhage. Control of bleeding during and after surgery is a very important determinant of surgical morbidity in this population.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Exact dosing regimens were tailored for each patient based on serial measurement of factor IX levels.

6.3.5 Directions for Use

Doses of IB1001 were administered such that factor IX levels were above 60%.

6.3.6 Sites and Centers

The trial was a multi-investigator, multicenter, international study, including sites different from the prior two substudies. Several U.S. sites were included.

6.3.7 Surveillance/Monitoring

Safety assessments were done as outlined in Tables 9-2 and 9-3 in the study report. Factor IX levels were determined before and after infusion. Duration of follow up was approximately one month, including inhibitory and non-inhibitory antibodies to factor IX as well as antibodies against CHO host cell proteins.

6.3.8 Endpoints and Criteria for Study Success

Criteria for efficacy success were determined by the surgeons' assessment of hemostatic control during and after the operation. Separate assessments for peri- and post-operative hemostasis were made. Safety was determined from reports of adverse events by subjects and investigators. Adverse events which occurred during the perioperative hospitalization were also included.

6.3.9 Statistical Considerations & Statistical Analysis Plan

Statistical plans for efficacy were limited to descriptive statistics and examination by the reviewer. A sample size of at least 10 surgeries in 5 subjects was derived from the CHMP Guideline on the Clinical Investigation of Recombinant and Human Plasma-Derived Factor IX Products (EMEA/CHMP/BPWP/144552/2009, 23 July 2009). These references are confirmed on pages 7 and 17 of the CHMP document.

6.3.10. Results

6.3.10.1 Populations Enrolled/Analyzed

Only major surgical cases were considered. The procedures performed are listed in Table 10-1 of the study report. Sixteen surgeries in 14 subjects were included in the report. All subjects enrolled were analyzed. Other than surgery, the inclusion and exclusion criteria were the same as the treatment protocols. One patient was enrolled but improved so much after a single dose of IB1001 that the surgery was cancelled.

6.3.10.1.1 Demographics

The demographics are presented in Table 11-1 in the study report. The cohort consisted of 13 males and 1 female. Mean age was 32 years with median of 33 years. The youngest subject was 12 years old. Approximately one third of the subjects were Asian.

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

The efficacy of IB1001 to control bleeding during surgery was evaluated according to the surgeon's assessment of the: a) estimated blood loss intra-operatively (less than expected, expected or more than expected) and b) post-operative blood loss (defined as superior hemostasis, adequate hemostasis or poorly controlled hemostasis).

Surgery phase analyses included 14 subjects who underwent 16 major surgeries. The types of procedures are listed in Table 10-1 adapted from the BLA Clinical Study Report. Perioperative Factor IX replacement was by bolus infusion in 11 major procedures and by continuous infusion in 5 procedures.

Subjects who received bolus infusions received an initial pre-surgery dose of 42-125 IU/kg with subsequent dosing from 32-62 IU/kg. The average adjusted recovery was calculated to be 0.95. Continuous infusion subjects received initial bolus doses ranging from 66-109 IU/kg with continuous infusion doses from 3-9 IU/kg/hr. Factor IX activity levels ranged generally between 50-120%.

Hemostasis control and blood loss were considered adequate or better in all procedures and acceptable Factor IX levels were achieved in the peri-, intra-, and post-operative periods with no requirements for transfusion support during surgery.

Table 10-1: Surgery Sub-study Subject Disposition

Disposition	n
Enrolled	15
Received IB1001	15
Completed procedures	14
arthroscopic synovectomy	1
open synovectomy	1
open inguinal hernia repair	1
elbow arthroplasty	2
knee arthroplasty	6
bilateral knee arthroplasty	1
hysterectomy/oopherectomy	1
ankle (tibiotalar) fusion	1
percutaneous Achilles lengthening	1
debridement of infected sinus over knee	1
Analysis Population	
Safety	15
Intent-to-treat	14
Study Phase Completion	
Completed (surgery sub-study only)	5
Ongoing (continued treatment with IB1001 after surgery sub-study)	9

Table 14-1: Summary of Blood Loss During and after Surgery by Regimen

Time of Blood Loss Assessment Outcome	Bolus Dosing N=11 n (%)	Continuous Infusion N=5 n (%)	All N=16 n (%)
At time of surgery			
Less than expected	4 (36.4)	2 (40.0)	6 (37.5)
Expected	7 (63.6)	3 (60.0)	10 (62.5)
More than expected	0	0	0
12 hours post surgery			
Hemostasis superior	3 (27.3)	1 (20.0)	4 (25.0)
Hemostasis adequate	8 (72.7)	4 (80.0)	12 (75.0)
Hemostasis poorly controlled	0	0	0
24 hours post surgery			
Hemostasis superior	3 (27.3)	1 (20.0)	4 (25.0)
Hemostasis adequate	8 (72.7)	4 (80.0)	12 (75.0)
Hemostasis poorly controlled	0	0	0
Transfusion required during surgery			
Yes	0	0	0
No	11 (100.0)	5 (100.0)	16 (100.0)

6.3.12 Safety Analyses

6.3.12.1 Methods

Screening and perioperative assessments are provided in Tables 9-2 and 9-3, respectively, in the study report. The quality of life assessments were not done for this subset. Safety assessments included reports of adverse events by investigators and subjects.

6.3.12.2 Overview of Adverse Events (AEs)

Overall exposure to product in the surgery substudy was presented in Table 3 from the Summary of Clinical Safety.

The adverse events were presented in Table 12-2 of the study report. Three adverse events reported as severe included perioperative pain, preexisting arthritis, and bleeding. Bleeding is an efficacy endpoint and was not considered in safety analysis. The remaining adverse events were all mild. The most common AE was procedural pain, which was not related to IB1001. Although continuous infusions were used in fewer subjects than bolus dosing, AEs were associated with continuous infusion (3 subjects, 17 AEs) more frequently than bolus dosing (11 subjects, 9 AEs). These AEs were largely pain and bleeding and are not considered related safety issues of IB1001. Fever occurred in three subjects. Other expected events such as nausea, vomiting, diarrhea, and back pain occurred in one person each. There were no unexpected safety signals.

6.3.12.3 Deaths

There were no deaths in clinical trial IB1001-01.

6.3.12.4 Nonfatal Serious Adverse Events

None.

6.3.12.5 Adverse Events of Special Interest (AESI)

Events of special interest included thromboses, hemolysis, transmitted infections, and immunogenicity. Other than immunogenicity, no AESI occurred during the perioperative surgery substudy.

Two subjects from the surgical study also demonstrated antibodies to CHO host cell proteins at study exit. No specific clinical sequelae were noted in these patients.

7. Integrated Overview of Efficacy

7.1 Methods of Integration

A total of 77 subjects were enrolled in one or more study phases and 68 of these subjects were used for analysis of safety and efficacy in the treatment phase. Overall, IB1001 is effective in preventing bleeding in hemophilia B subjects.

7.2 Demographics and Baseline Characteristics

The baseline characteristics of the substudy populations are sufficiently alike that pooling data for safety is reasonable. The efficacy targets for each substudy are all different, so the efficacy data and the individual indications are best evaluated separately.

7.3 Efficacy Conclusions

IB1001 is equally effective as licensed BeneFIX in all studies.

8. Integrated Overview of Safety

8.1 Safety Assessment Methods

The population undergoing integrated analysis of safety is the population from the three substudies of the single study IB1001-01.

The safety issues of interest were adverse events in general, thrombogenicity, inhibitors, and formation of antibodies to CHO host cell proteins. The integrated safety population includes all subjects in all phases. Since all safety assessments were descriptive, no additional methods were required to pool them together.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The overall disposition of study subjects is provided in section 6.2.10.1.3. Four substudies (PK, treatment, surgery, continuation) were used to evaluate safety.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Study enrollment closed in May 2011. A total of 77 subjects were enrolled. As of April 2012, 20 subjects had received over 100 exposures each and 52 subjects had received over 50 exposures each.

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

Based upon Table 4 from the Summary of Clinical Safety and the demonstration of similarities in the subpopulation patient characteristics, it is reasonable to pool the data together as the applicant has done.

8.4 Safety Results

In 18 subjects, development of antibodies against host cell proteins led to placement of ongoing studies on clinical hold.

8.4.1 Deaths

There were no fatalities in this trial.

8.4.2 Nonfatal Serious Adverse Events

Table 10 in the Summary of Clinical Safety presented all of the SAEs in the trial. The data and narratives indicate that these SAEs were unrelated to the product administration.

8.4.3 Study Dropouts/Discontinuations

Eight subjects withdrew or discontinued from any phase of the trial. On October 15, 2012, an information request was made for narratives and other information regarding these subjects. This information came in as part of amendment #09. Most subjects withdrew for reasons that were unrelated to IB1001. Subject (b) (6) had expressed some dissatisfaction with the control of bleeding with the product. Numerous bleeding episodes were documented, some with control rated as fair or poor, with more recent episodes demonstrating a trend towards poorer performance. His assays for anti-FIX and anti-CHO were negative at all time points. The remaining narratives did not indicate any issue with IB1001.

8.4.4 Common Adverse Events

Table 10: All Adverse Reactions (Product-Related and Unrelated) that Occurred in ≥ 5% of Study Subjects (PTPs)

MedDRA System Organ Class	Adverse Reaction	Number of Patients (%)[1]
Nervous system disorders	Headache	10 (14.7)
	Dizziness	5 (7.4)
General disorders and administration site	Pyrexia	9 (13.2)
Psychiatric disorders	Insomnia	5 (7.4)
Infections and infestations	Nasopharyngitis	5 (7.4)
Gastrointestinal disorders	Diarrhea	5 (7.4)
	Vomiting	4 (5.9)
Musculoskeletal and connective tissue disorders	Arthralgia	4 (5.9)
	Back pain	
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	4 (5.9)

[1] The percent is calculated relative to 68 subjects who participated in the treatment study phase.

The frequency of adverse events per subject in Table 10 above as well as the frequencies of drug-related adverse reactions in Table 11 below.

Table 11: Summary of Study-Drug Related Adverse Events*

MedDRA Preferred Term	Number of Events
Headache	23 (8.7)
Apathy	1 (0.4)
Depression	1 (0.4)
Dysgeusia (metallic taste)	1 (0.4)
Flu symptoms	1 (0.4)
Hemophilia (exacerbation)	1 (0.4)
Injection site discomfort	1 (0.4)
Lethargy	1 (0.4)
Weakness	1 (0.4)

* Classified as at least possibly product-related

8.4.5 Clinical Test Results

No safety signals were seen in the routine laboratory results, physical examinations, or vital signs. The results of immunogenicity studies are given in section 8.5.

8.4.6 Adverse Events of Special Interest

Events of special interest included thromboses, hemolysis, transmitted infections, and immunogenicity. No episodes of thrombosis, hemolysis, or product-transmitted infection occurred during any part of the trial.

8.5 Additional Safety Evaluations

8.5.1 Immunogenicity (Safety)

There was no pattern of increased consumption of product, the absence of which is evidence against clinically significant immunogenicity mediated by neutralizing antibody against the therapeutic protein.

Time to development of antibodies against host cell proteins is given in figure 1 below. Titers as high as >300,000 were noted (subject (b) (6)). Increasing titers were reported in numerous subjects. Review of the narratives does not show any clinical adverse events related to the antibody formation.

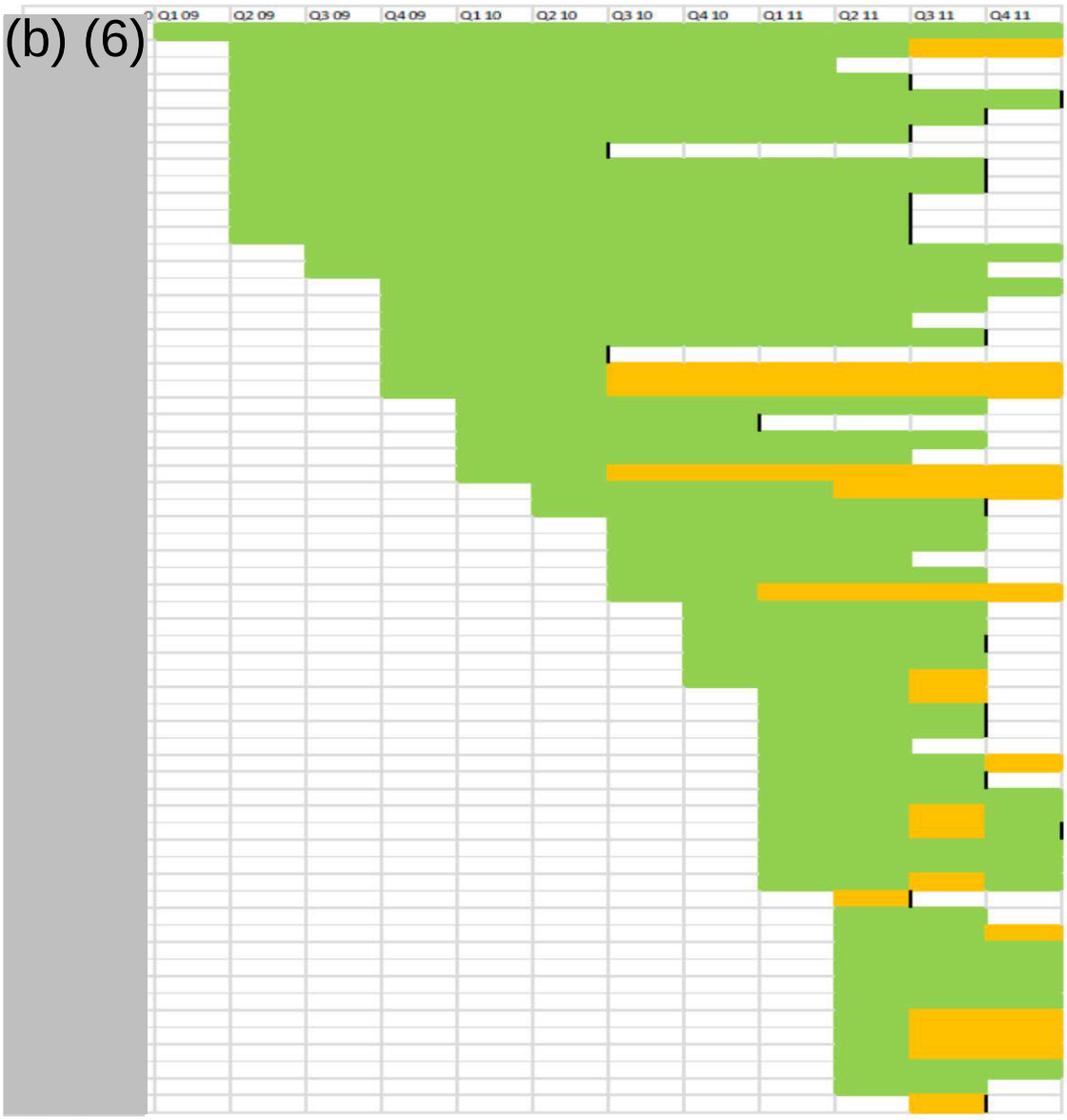


Figure 1: Study IB1001-01: Subjects time in study (green); subjects tested positive for anti-CHO protein (yellow) Adapted from 0061_responsetoinforequest.pdf, p. 12

The following table shows the results for subjects who were positive for non-inhibitory anti-FIX antibodies at the conclusion of the trial.

Sample of Patients Positive for Non-inhibitory Anti-FIX antibodies, including all Three Who Were Positive at Conclusion

Patient ID	Reference	Inhibitory anti FIX BU/ml	Non-inhibitory anti-FIX
(b) (6)	05/11/2009	Negative	Negative
	06/13/2009	Negative	Negative
	09/16/2009	Negative	Negative
	12/17/2009	Negative	Positive
	03/10/2010	Negative	Negative
	06/20/2010	Negative	Negative
	10/14/2010	Negative	Positive
	01/05/2011	Negative	Positive
	03/13/2011	Negative	Positive
	05/11/2009	Negative	Negative
	06/02/2009	Negative	Negative
	07/22/2009	Negative	Negative
	09/16/2009	Negative	Negative
	12/17/2009	Negative	Positive
	03/17/2010	Negative	Negative
	06/28/2010	Negative	Negative
	09/19/2010	Negative	Positive
	12/29/2010	Negative	Positive
	03/24/2011	Negative	Positive
	06/2011	Negative	Positive
	04/2010	Negative	Positive
	08/26/2010	Negative	Negative
	12/03/2010	Negative	Negative
	03/10/2011	Negative	Negative
	09/21/2011	Negative	Negative
	12/14/2011	Negative	Positive

[Adapted from Attachment 3, IND 13551, A061, p. 3; Amendment 9, BLA 125426.]

8.6 Safety Conclusions

Eighteen subjects out of 68 developed antibodies against CHO host cell proteins. Some of these titers were increasing and/or quite high. No clinically significant adverse reactions could be ascribed to these antibodies, though the long-term consequences are unknown.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Not studied.

9.1.2 Use During Lactation

Not studied.

9.1.3 Pediatric Use and PREA Considerations

The company has requested a pediatric waiver for children less than one month. They also requested a deferral for less than two years because they anticipate difficulty in enrolling these subjects. No post-market commitments have been made. No issues of differential safety or efficacy were identified in the pediatric patients in the studies.

9.1.4 Immunocompromised Patients

Not studied.

9.1.5 Geriatric Use

Not applicable because of younger age of this population.

10. Conclusions

IB1001 was found to be effective in treatment and perioperative populations. In 18 subjects, development of antibodies against host cell proteins led to placement of ongoing research studies on clinical hold.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hemophilia B is a rare condition with variable deficiency of coagulation factor IX. • Hemophilia is accompanied by bleeding into tissues and joints which can be spontaneous, post-traumatic, or perioperative. • Bleeding can be acutely devastating, such as intracranial bleeding, or chronically destructive such as hemophilic arthropathy.	• Hemophilia B is a serious, progressive, life-threatening disease. • The bleeding associated with hemophilia can cause clinically significant complications. • Current treatment is expensive and carries risks of infection or adverse reactions.
Unmet Medical Need	• There is one other recombinant factor IX product licensed for use by FDA. • Numerous other plasma-derived factor IX products exist, but carry the same risks as other human plasma products, such as infection with known or future agents, acute hypersensitivity reactions, or immunogenicity with resistance.	• Although alternative recombinant therapy exists for Hemophilia B, it is expensive with the average on-demand treatment costing ~$130,000/year and even higher costs for those on prophylactic therapy. Increasing the number of available licensed products could have a positive impact and allow options for hemophilia patients who remain untreated due to high costs.
Clinical Benefit	• IB1001 was shown to be effective for treatment of, and prevention against spontaneous or traumatic bleeding by both prophylactic or on-demand regiments • IB1001 was shown to be effective in the perioperative setting for reduction of bleeding during surgery.	• IB1001 is equally effective as the currently licensed recombinant product.
Risk	• Seventeen or eighteen (depending on interpretation of baseline) subjects developed antibodies to CHO host cell proteins. In some patients, the titers were increasing and/or quite high. • No clinical sequelae were noted separable from the bleeding inherent in the underlying disease. • The long term consequences of high or increasing titers of anti-CHO antibodies is unknown though cross-reactivity with innate proteins is a concern.	• The risks of long-term exposure to immunogenic proteins with increasing or very high titers are largely unknown but theoretically could include allergic reactions, anaphylaxis, serum sickness, autoimmunity, and immunogenicity.
Risk Management	• If IB1001 were approved with the current frequency of anti-CHO antibody formation, studies would be necessary to comprehensively understand the cause of the immunogenicity, what influences the formation of antibody in only some recipients, the acute consequences of the CHO protein, and the long-tem sequelae of the reactivity and possible immune-complex deposition and cross-reactivity.	• A number of studies would be needed to understand aspects of the process of immunogenicity development. • Recipients would need to be frequently evaluated in order to monitor for reactivity and complications, many of which are unknown at this point resulting in broad surveillance.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Summary and Assessment

IND 13551 was placed on clinical hold due to the presence of impurities that led to the development of anti-CHO antibodies that were increasing in titer in 25% of affected subjects. The presence of these antibodies was considered a potential safety issue with insufficient information to assess potential clinical significance. Although anti-CHO antibodies have been observed in other factor products, prior findings were transient with a lower frequency. The CMC review observed CHO impurities visible on (b) (4) that require removal as part of a manufacturing change prior to product approval.

The anti-CHO antibodies were described as non-neutralizing IgG which alone might not be problematic but with repeated exposure and continued stimulation of the immune response could have the potential to result in formation of IgE antibodies with severe allergic responses. Non-inhibitory anti-FIX antibodies also developed during the trial in 3 subjects. The possibility exists that repeated immune stimulation could eventually lead to inhibitory antibodies.

The CHO impurity co-purified with IB1001 was subsequently identified as (b) (4) The structural similarities resulting in co-purification suggest that anti-CHO antibodies also have the potential to cross-react with human tissues or human (b) (4) Cross-reactive antibodies have the potential to lead to autoimmune disorders as well as interfere with the numerous functions of (b) (4) which include cell adhesion, growth, differentiation, and wound healing. Due to the unknown clinical significance as well as the availability of other licensed Factor IX products, the risks were considered to outweigh the benefit of this product prior to its manufacturing improvements.

11.2 Discussion of Regulatory Options

Regulatory options were discussed to address the development of immunogenicity against host cell proteins and the potential risk for adverse reactions. Options included increased surveillance of subjects, and limitation of study drug administration to certain subsets of subjects.

11.3 Recommendations on Regulatory Actions

The ongoing studies were placed on clinical hold. Given the availability of licensed FIX products, the risk to research subjects was determined to exceed the benefits.

11.4 Labeling Review and Recommendations

A labeling review with recommendations is not applicable at this time pending manufacturing changes detailed in the complete response letter.