Health Service

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

STATISTICAL REVIEW AND EVALUATION BLA

FINAL

BLA/Supplement Number:	125426/0
Product Name:	IB1001
Indication(s):	Control and prevention of bleeding episodes and peri-operative management in patients with hemophilia B
Applicant:	Inspiration Biopharmaceuticals, INC.
CBER Receipt Date:	4/6/2012
Review Priority:	Standard
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1. Executive Summary

Study IB1001-01 including a PK phase, a treatment phase and a surgical substudy was conducted to support the licensure of IB1001, an intravenous recombinant factor IX for control and prevention of bleeding episodes and peri-operative management in patients with hemophilia B.

Descriptive analysis was used for most of the primary efficacy endpoints. The primary analysis results are reproducible except for the annualized bleeding rate in Table 11.4-7. The sponsor is not able to address this issue within the review cycle. In addition, the sponsor's approach to calculate the study duration using the study cutoff date is problematic as no data was reported from the last visit to the cutoff date for some subjects. These two issues will be repeated in the CR (Complete Review) letter. The decision of CR letter was made by the review committee mainly because of the development of antibodies against CHO host cell proteins.

2. Background

Hemophilia B is an inherited congenital tendency of males to bleed caused by a deficiency of factor IX. Currently there is one marketed recombinant factor IX, BeneFIX by Wyeth approved on February 11, 1997.

The sponsor is developing IB1001, an intravenous recombinant factor IX for control and prevention of bleeding episodes and peri-operative management in patients with hemophilia B. The original IND 13551 was submitted to FDA on Nov 13, 2007. In the End-of-Phase 2 meeting held on October 14, 2010, FDA and the sponsor confirmed that the sponsor is not seeking a prophylaxis indication. The original BLA was submitted on April 6, 2012.

On May 30, 2012, the sponsor reported the development of antibodies against CHO host cell proteins (HCP) in 18 out of 68 patients who were treated with IB1001 under IND 13551. On July 5, 2012, FDA placed IND 13551 on clinical hold. However, the BLA review process was not stopped. Because the sponsor is not able to fully resolve above issue within this review cycle, FDA will issue a CR letter.

On October 11, 2012, FDA sent an IR (Information request) letter to the sponsor including two statistical comments. FDA received the sponsor's responses on December 4, 2012. However, the sponsor indicated that they needed more time to address the first comment (See page 11 of this review).

This is an eCTD submission. The link to access the .enx file is:

(b)(4)

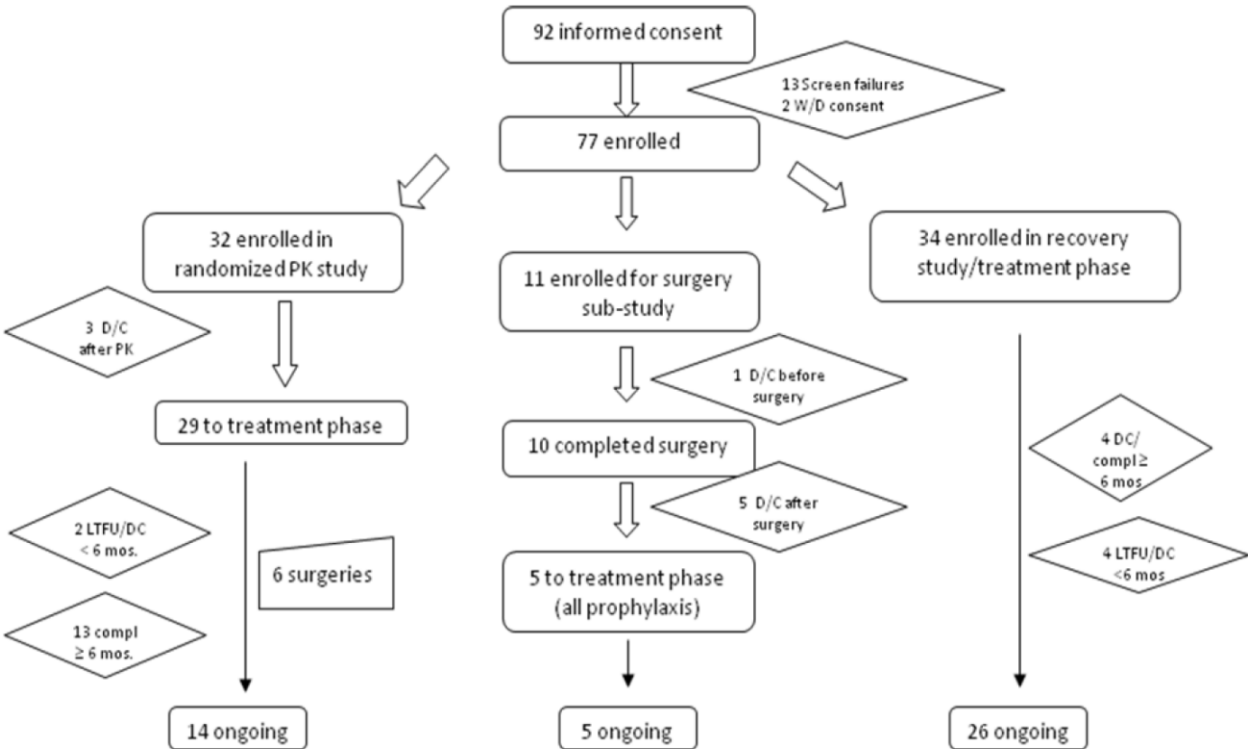
3. Clinical Studies

The sponsor's strategy for clinical development of IB1001 is summarized in Table 1 below. ED represents for exposure day.

Table 1. IB1001 Clinical Development (Sponsor's Table 1 in Module 2)

Study No.	Study Purpose	Study status
IB1001-01 (PK phase)	Pharmacokinetics in subjects ≥12 yrs	complete
IB1001-01 (Treatment phase)	Safety and efficacy of IB1001; treatment for at least 50 ED	50 subjects for 50 ED , completed
IB1001-01 (Continuation phase)	Long term safety and efficacy of IB1001; up to 100 ED	50 subjects for 100 ED – post-approval commitment; ongoing
IB1001-01 (Surgical substudy)	To evaluate the ability of IB1001 to provide coverage against bleeding under surgical circumstances	completed for 16 procedures in 14 subjects
IB1001-02	PK, safety and efficacy in previously treated children 0-12 years of age for at least 50 exposure days	ongoing; post-approval commitment
IB1001-03	Safety and efficacy in previously untreated children <6 years of age (treatment for up to 3 years or 100 ED)	not yet initiated; post-approval commitment

This review memo covers the PK, treatment and surgery phases of study IB1001-01. The protocol was designed as a Phase I/II/III study in order to minimize the need to switch patients between factor IX products multiple times. The following flow chart from sponsor's module 2 shows the status of subjects as of the data cut-off date (December 21, 2011). The cut-off date was selected to assure that it included a minimum of 50 subjects with 50 ED.



3.1. IB1001-01 (PK phase)

3.1.1. Protocol description

It was a randomized, double-blind, cross-over design using BeneFIX as comparator to evaluate the PK of IB1001 in subjects with severe hemophilia B who had received at least 150 prior exposures to a factor IX preparation.

Subjects were assigned in random order to receive either a single intravenous 75 ± 5 U/kg dose of BeneFIX or IB1001. Factor IX levels were determined pre-infusion and at certain time points post-infusion. A washout of 5-28 days was applied between two treatments.

PK parameters included half-life ($t_{1/2}$), in vivo recovery (IVR), maximum plasma concentration (C_{max}), $AUC_{(0-\infty)}$, *etc*.

A comparison of IB1001 and BeneFIX was performed through the calculation of the lower 1-sided 95% confidence interval (CI) for the $AUC_{(0-\infty)}$ ratio of IB1001 over BeneFIX (calculated on a log scale and then untransformed). Non-inferiority was declared if the lower 1-tailed 95% CI was above 80%.

3.1.2. Disposition of patients

The PK phase of study IB1001-01 was initiated in February 2009 and completed in September 2010. It was conducted at 11 institutions in the USA, Israel, UK, and Italy.

Thirty two subjects (17 subjects in BeneFIX/IB1001 sequence; 15 subjects in IB1001/BeneFIX sequence) were enrolled and all subjects were randomized and completed both study periods.

3.1.3. Demographic and other baseline characteristics

The demographic and baseline characteristics regarding age, race, baseline level of factor IX were comparable between the two treatment sequences.

3.1.4. Study results

The lower bound of the 1-sided 95% CI for the $AUC_{0-\infty}$ ratio of IB1001 over BeneFIX was 90%; therefore, the primary endpoint of non-inferiority was established. The PK parameters by treatment groups are presented in Table 2 below.

Table 2. Pharmacokinetic Parameters of BeneFIX and IB1001 (Sponsor's Table 11.4-1)

Parameter	BeneFIX N=32	IB1001 N=32
Alpha-phase half-life (hr)		
mean ± SD	10.4±1.7	9.6±2.7
median	10.2	9.9
range	7.0-14.7	2.8-14.3
Beta-phase (terminal) half-life (hr)		
mean ± SD	33.4±21.2	29.7±18.2
median	27.9	25.8
range	17.5-126.7	13.2-118.4
$AUC_{0-\infty}$ (IU/dL/hr)		
mean ± SD	1723±465	1674±605
median	1680	1601
range	1061-3170	886-3682
AUC_{0-t} (IU/dL/hr)		
mean ± SD	1419 ±340	1401±367
median	1366	1399
range	969-2317	831-2188
Clearance (L)		
mean ± SD	0.05±0.01	0.05±0.02
median	0.04	0.05
range	0.02-0.07	0.02-0.08
Mean residence time (hr)		
mean ± SD	39.7±18.7	35.9±18.5
median	35.3	31.7
range	23.9-114.9	18.4-124.4
Volume of distribution-steady state (mL/kg bodyweight)		
mean ± SD	180±70	160±40
median	170	160
range	90-480	90-290
C_{max} (unadjusted recovery) (IU/dL)		
mean ± SD	72.5±17.0	74.0±17.1
median	70	70
range	46-112	51-113

3.2. IB1001-01 (treatment phase)

3.2.1. Protocol description

The treatment phase of IB1001-01 was a multicenter, non-randomized, open-label study on subjects with severe hemophilia B who had received at least 150 prior exposures to a factor IX preparation. Completion of the above PK study or the IB1001 recovery study (for those subjects who did not participate in the PK study) was a necessary condition for participation in the treatment phase.

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. The analysis was performed after documentation that at least 50 subjects had been treated for at least 50 ED.

The type of treatment (prophylaxis or on-demand) that the subject received was at the discretion of the investigator and the desire of the subject. Subjects were permitted to switch between treatment types. The planned prophylaxis regimen was an intravenous 50-75 IU/kg dose of IB1001 twice a week. For subjects in the on-demand arm, at the time of a bleeding episode, subjects received an intravenous dose of 50-100 U/kg of IB1001, with the dosage determined by the investigator.

At the conclusion of the treatment phase (6 months or approximately 50 ED), subjects were invited to continue to receive IB1001 as part of the continuation study. The continuation study is ongoing with the goal of following 50 subjects for 100 ED, which is a post-approval commitment in the EU.

Safety and efficacy data were collected every 3 months. Throughout the study, subjects maintain a diary to record information about each infusion, any AEs, and bleeding episodes. Within 6 hours after the subject believes the bleeding has stopped, he is instructed to provide an overall evaluation of efficacy of treatment using verbal descriptors: excellent, good, fair and poor.

At each three-month visit the investigator makes a single assessment of the control of bleeds that occurred during the period. The investigator indicates his/her overall assessment of product efficacy with categories of “effective”, “partially effective”, “not effective”, and “not applicable”.

The primary efficacy variables were control of breakthrough bleeding during prophylaxis and control of hemorrhaging during bleeding episodes in either the prophylaxis or on-demand treatment regimens.

Annualized bleeding rates were to be evaluated for subjects in the prophylaxis and on-demand regimens with rates calculated as:

annualized bleeding rate = (# of bleeding episodes x 12) / (# months of observation).

Annualized bleeding rate was compared between the prophylaxis and on-demand regimens by t-test.

Safety data were monitored by an independent DSMB. Subjects were monitored for the presence of inhibitory and non-inhibitory antibodies before the first infusion of IB1001, after the first 5 ED to IB1001, and at each three month study visit.

Safety Population: all subjects who received at least 1 dose of IB1001.

Intent-to-Treat (ITT) Population: all subjects who enrolled in the treatment phase of the trial.

3.2.2. Disposition of patients

Table 4 summarizes the disposition of the 68 subjects who are the basis of the safety and efficacy analyses of IB1001 treatment phase.

Table 3. Disposition of Subjects in Treatment/Continuation Phase (sponsor's Table 10.1-2)

	Prophylaxis	On-demand
Enrolled	59	9
Treated	59	9
Analysis Population		
Safety	59	9
Intent-to-treat	59*	9
Study Phase Completion		
Completed	13	2
Discontinued (Treatment or Continuation)	8	0
Ongoing (Continuation)	38	7
Reason for Premature Discontinuation		
Withdrew consent	2	NA
Investigator discretion	1	NA
Other	5	NA

Subject (b)(6) was enrolled as a "targeted prophylaxis" subject, but he was included in the on-demand arm due to the low infusion frequency indicated from his infusion log. Five subjects left the treatment phase prior to completing six months.

3.2.3. Demographic and other baseline characteristics

Most of the subjects were Caucasian with a mean age of 30 years and average age at diagnosis of 2.3 years. With one exception (subject (b)(6)), all subjects had baseline factor IX levels ≤2 IU/dL.

3.2.4. Study results

3.2.4.1. Prevention and control of bleedings

Thirty-seven of 63 subjects who were on prophylaxis regimens for all or part of their treatment (59 enrolled and 4 switched from on demand) and all subjects who were on on-demand regimens for all or part of their treatment reported bleeding episodes.

For each bleeding episode, subjects were asked to rate the efficacy of IB1001 to treat the bleeding episode (Tables 4 and 5). However, for some of the bleeding episodes reported in 2009, no subject assessment of efficacy was recorded due to misunderstanding between the sponsor and the CRO.

Table 4. Subject Assessment of Efficacy of IB1001 (Sponsor's Table 11.4-2)

	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)

Table 5. Infusions Required for Treatment (Sponsor's Table 11.4-3)

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

Of 235 subject visits where the efficacy of IB1001 was evaluated by investigators for the preceding three month period, 222 (95%) three month periods were rated as "effective" prevention and treatment of bleeding by IB1001. Three 3-month intervals (1%) were rated as 'not applicable', eight (3%) as "partially effective" and two (1%) as "requires further evaluation".

3.2.4.2. Annualized bleeding rates

Some subjects switched between on-demand and prophylaxis regimens; in those instances the subject was counted in the appropriate regimen during the time he was receiving that regimen.

Table 6. Summary of Annualized Bleeding Rates (sponsor's Table 11.4-7)

	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

3.2.4.3. Dropouts or Missing Data

Of the 68 subjects who entered the treatment phase of study IB1001-01 five subjects withdrew or were lost to follow up prior to completion of six months of treatment (see Table 7 below)

Table 7. Subjects withdrew or lost to follow up <6 months

ID	Description of infusions and bleedings	Efficacy analysis
(b)(6)	Left the study very early, recorded 6 prophylaxis infusions, had one bleeding without assessment of efficacy	Excluded
(b)(6)	Did not return home infusion diaries and has no documentation of any prophylaxis infusions	Excluded
(b)(6)	Did not return home infusion diaries and has no documentation of any prophylaxis infusions	Excluded
(b)(6)	Completed at least 25 exposure days but left before completing six months of treatment	Included
(b)(6)	Completed at least 25 exposure days but left before completing six months of treatment	Included

3.2.4.4. Examination of Subgroups

The sponsor did not performed formal subgroup analyses. Pediatric subjects (<18 years) generally had annualized bleed rates ≤3; exceptions included one subject who was very poorly compliant with the prescribed twice weekly infusions ((b)(6)) and two subjects on once weekly regimens ((b)(6)

3.2.4.5. Safety Evaluation

There have been no deaths in study IB1001-01.

For the 47 subjects in the prophylaxis regimen for at least six months, and the four subjects in the on-demand who have accumulated more than 50 ED, no development of

inhibitory antibodies was detected. On May 30, 2012, the sponsor reported the development of antibodies against CHO host cell proteins (HCP) in 18 out of 68 patients who were treated with IB1001.

3.3. IB1001-01 (surgery)

The surgery sub-study was a non-randomized, open-label design to evaluate the ability of IB1001 to provide coverage against bleeding under surgical circumstances. Subjects were allowed to participate in the surgery sub-study only, without participation in the other phases of study IB1001-01. Use of either bolus or continuous infusion is permissible for support of major surgeries.

A minimum of 10 surgical cases in at least 5 subjects was required; as of September 2011, 16 surgeries had been completed in 14 subjects. Most were Caucasian with a mean age of 32 years.

Efficacy of IB1001 for support of major surgery was based on the surgeon's assessment of efficacy including: a) estimation of blood loss as "less than expected", "expected", or "more than expected" at the time of surgery; and b) at 12 and 24 hours post-surgery assessment of hemostasis as "hemostasis superior", "hemostasis adequate", or "hemostasis poorly controlled".

Among the 16 surgeries, 6 (37.5%) of them were rated as "less than expected" regarding blood loss by the surgeons' assessment, and the rest 10 were rated as "expected". Four (25%) surgeries were rated as "hemostasis superior" at both 12 and 24 hours post-surgery assessment of hemostasis, and the rest 12 were rated as "hemostasis adequate" at both time points.

4. Communications with the sponsor

On October 11, 2012, FDA sent an IR letter to the sponsor including the following two statistical comments. FDA received the sponsor's responses on December 4, 2012.

1) We are not able to replicate your results for the annualized bleeding rate in Table 11.4-7 using the variables "PBLDR" and "OBLDRT" in dataset "bld2.xpt", though we understand that you modified your SAS program to recalculate time on prophylaxis and on-demand using the termination dates instead of the data cut-off date (December 21, 2011). Please clarify in details how you derived the annualized bleeding rate in Table 11.4-7 and provide all the necessary datasets for FDA to conduct analysis (e.g., datasets under your library name "clinical").

<u>Sponsor's response:</u>

We have been unable to obtain this information within the time frame required by the Agency for this response. We will continue to seek clarification from the contracted statistician involved in the study. It is planned to complete the response at a later date as part of the restructuring of the company under Chapter 11 bankruptcy.

2) Related to above item, in dataset "bld2.xpt", it seems that the prophylaxis total time (variable "pttm") was calculated based on the difference of these two variables: "p1stdt" and "p1endt'. However, the last infusion date of treatment phase was much earlier than the "p1endt" in some cases. If subjects dropped out around the last infusion date, there should be more subjects with follow up time less than <6 months than you reported (5

subjects). For example, the following two subjects' last infusion date was around 3-4 months earlier than the end of prophylaxis date. Please clarify.

ID	P1STDT	P1ENDT	INFENDT
(b)(6)	11MAY2011	21DEC2011	02AUG2011
(b)(6)	11JUN2011	21DEC2011	15SEP2011

Sponsor's response:

The patients indicated above were continuing in the study as of the data cut of date (21 December 2011). The gap between "p1endt" and the last treatment infusion for some study subjects is a result of the study schedule, which requires subjects to be seen at the clinic approximately every three months.

Using Subject (b)(6) *as an example, the subject completed a scheduled three-month visit on September 16, 2011 with his last infusion the day prior to his visit. Since the subject had not been seen since September 2011, there would no diary data available for the subject since that date. Note that it would be possible to calculate annualized bleed rates for study subjects with a cut-off date of their last infusion day for subjects on prophylaxis, but this would not work for subjects' on-demand since they only infuse at the time of a bleeding episode. Therefore, as a general rule, for subjects who were ongoing at the time of the data cut-off, the data cut-off was used as the end of the observation period.*

Data monitoring and collection is ongoing for the study. The timing of the next data cut-off has not yet been defined.

5. Conclusions and recommendation:

1) The sponsor's primary analysis results are reproducible except for the annualized bleeding rate in Table 11.4-7.
2) In the treatment phase of study IB1001-01, a total of five subjects switched treatment types, mostly from on demand to prophylaxis. These subjects had a lower bleeding rate after switching to prophylaxis. They did not have a significant impact on the efficacy analysis if they were included in their original assigned group.
3) There were a total of 11 pediatric subjects (<18 years old) and 54 adults included in the efficacy analysis in the treatment phase of study IB1001-01. This reviewer's subgroup analyses show that the primary efficacy results are comparable between pediatric subjects and adults.
4) Due to the lack of study success criteria in efficacy, statistical summaries are commented without a decisive conclusion.
5) No development of inhibitory antibodies was detected among the study subjects. This reviewer defers to the medical reviewer for thorough safety review.
6) The sponsor's responses to the two statistical comments were not satisfactory and they will be repeated in the CR letter.

6. Comments to the sponsor to be included in the CR letter:

We have reviewed your responses to the two statistical comments included in the October 11, 2012 IR letter.

1.) Regarding the first statistical comment that we are not able to replicate your results for the annualized bleeding rate in Table 11.4-7, we recognize that you need more time to obtain necessary information to address the issue. Please submit your clarification to the Agency as soon as you obtain relevant information to resolve it.

2.) Regarding the second comment, it is not appropriate to use the cutoff date to calculate the annualized bleed rates because the bleeding events occurred between the last visit and the cutoff date cannot be captured in the calculation for some subjects; therefore, the annualized bleed rate can be underestimated. FDA's original comment did not suggest using the last infusion date either as it would not work for the study period without infusions. We recommend that the annualized bleed rate should be calculated based on the longest study period with bleeding information available. For example, for Subject (b)(6), the last visit date of September 16, 2011 should be used instead. Please submit the updated analysis.

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