DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

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

STATISTICAL REVIEW AND EVALUATION BLA

SECOND CYCLE FINAL MEMO

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.
Receipt Date of Original BLA: **CR letter Issued Date:** **Receipt Date of CR Response**	4/6/2012 2/1/2013 1/27/2014
Review Priority:	Standard
Statistical Branch:	Therapeutics Evaluation Branch
Primary Statistical Reviewer:	Chunrong Cheng, Ph.D., Visiting Scientist
Concurring Reviewer:	Renee Rees, Ph.D., Team Leader
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Committee Chair	Chava Kimchi-Sarfaty, Ph.D.
Clinical Reviewer(s):	Irwin Feuerstein, MD
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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.

During the review of the original BLA, the reported annualized bleeding rate (ABR) was not reproducible. In the response to the complete response (CR) letter dated February 1, 2013, ABRs have been recalculated using a more current data cut-off and a revised annualized bleeding rate definition. The updated results of ABR are now reproducible. A statistically significant difference in the mean ABR (after square-root transformation) between subjects receiving prophylaxis and those treated on-demand was observed.

After the mid-cycle review, FDA requested the applicant to report ABRs based on the original scale, instead of the square-root transformed scale. The applicant does not agree and argues that it is a pre-specified analysis. A further comment will be sent out to reiterate that data transformation may be acceptable in statistical analysis, but the final reporting should be based on the original scale to avoid misunderstanding, especially in the label.

A second CR decision was made based on the review of other disciplines, and the above comment will be included in the CR letter.

2. Background

Hemophilia B is an inherited congenital tendency of males to bleed caused by a deficiency of factor IX.

The applicant has developed 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 November 13, 2007. The original BLA was submitted on April 6, 2012.

On May 30, 2012, the applicant 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.

A CR letter was issued on February 1, 2013. During the statistical review of the BLA, the primary analysis results were reproducible except for the annualized bleeding rate (ABR) in Table 11.4-7 in the Safety and Efficacy Report (March 4, 2012, under Module 5). In addition, the applicant's approach for calculating the study duration using the study cutoff date was problematic. Specifically, the applicant used the variable "p1endt" as the last day to calculate the duration on prophylaxis, however, the last infusion date of the prophylaxis phase was much earlier than the "p1endt" date in some subjects, thus the ABR could be underestimated. It is not clear how the variable "p1endt" was derived. These issues were included in the CR letter as Items 21 and 22, respectively.

On April 16, 2013, the applicant notified the FDA that Cangene acquired the investigational hemophilia compound IBI001 from Inspiration.

Because the applicant implemented manufacturing process changes for drug substance to reduce the levels of HCP, the clinical hold of IND 13551 was removed on July 26, 2013. FDA indicated that the applicant was not required to conduct an efficacy study to support licensure of the

modified process, instead, a single-dose adult safety and PK study of at least 20 naive subjects may be adequate to demonstrate comparability to the pre-modified process product.

The full response to the CR letter was received on January 27, 2014. In the next three sections, this review memo will describe the pivotal study IB1001-01, summarize the applicant's response to the above two CR comments (Items 21 and 22), and report the updated study analysis results (Section 5.3.5.2 in BLA) respectively. In this memo, tables without a source given are generated by this reviewer's independent analysis. All the analyses in this memo are based on the ITT population.

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(b) (4)

3. Introduction of Study IB1001-01

Study IB1001-01was designed as a Phase I/II/III study covering the PK, treatment and surgery phases.

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 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 initial analysis submitted in the original BLA was performed after documentation that at least 50 subjects had been treated for at least 50 exposure days (EDs). 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.

Safety and efficacy data were collected every 3 months. Throughout the study, subjects maintained 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 was 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 made a single assessment of the control of bleeds that occurred during the period. The investigator indicated 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. Descriptive analysis was applied on these variables.

Annualized bleeding rates were to be evaluated for subjects in the prophylaxis and on-demand regimens. The square-root transformed data with the 2-sample t-test were used to test for significant differences in the mean number of bleeding episodes between subjects receiving prophylaxis and those treated on-demand.

4. Response to statistical comments in CR letter

Item 21: 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.

Summary of response:

The IB1001-01 study report has been revised and updated, and a new data cut-off of March 01, 2013 has been applied to the IB1001-01 study to capture current efficacy and safety data. A new analysis of annualized bleeding rates with a revised definition of annualized bleeding rate has been completed. Updated IB1001-01 datasets, including Analysis Datasets, are submitted based on this updated clinical study report.

Item 22: It is not appropriate to use the cutoff date to calculate the annualized bleed rates because the bleeding events that occurred between the last visit and the cutoff date cannot be captured in the calculation for some subjects. Therefore, the annualized bleed rate can be underestimated. FDA's original comment did not suggest using the last infusion date as it would also not work for study periods without infusions. We recommend that the annualized bleed rate should be calculated based on the longest study period with bleeding information available. For example, the last visit date of September 16, 2011 should be used instead for Subject (b) (6). Please submit the updated analysis.

Summary of response:

The revised definition is as follows:

> "Annualized bleeding rates will be evaluated for subjects in the prophylaxis and on demand regimens in the treatment and continuation phases of study IB1001-01. If a patient switched regimens during the study, then separate annualized bleeding rates will be calculated for their time on each regimen. Rates will be calculated as:
>
> annualized bleeding rate = (# of bleeding episodes x 12) / (# months of observation)
>
> The number of bleeding episodes and the number of months of observation will be determined from the patient diary data. The months of observation will be calculated from the first date of the treatment phase to the last entry into the patient diary prior to the end of the study, or prior to the data cutoff date in the case of an interim analysis.
>
> Time on a commercial factor IX product during the clinical hold period will be excluded from the calculations"

Considering IB1001-01 is a long term study with multiple study phases, and some subjects were off IB1001 due to the clinical hold, the cutoff date for the annualized bleeding rate needs to be reviewed and defined in detail.

- For subjects who entered the treatment phase after participating in the PK Phase, the date of the final PK sample was used as the start of the treatment period. The only exception was subject (b) (6), who did not immediately enter treatment post-PK phase due to a surgery conducted off-study. This subject had a recovery study done prior to entry into the treatment phase. As a result, the date of recovery was used.

- For subjects who entered the treatment phase with a recovery study, the date of the recovery study was used as the start of treatment.
- For subjects who entered the treatment phase after initial enrolment into the surgery substudy, efforts were made to exclude the initial surgery treatment period.
- The last entry in the patient infusion diary prior to the data cut point of 2013-Mar-01 was used as the end of the treatment period.

5. Updated efficacy results

- **Treatment of breakthrough bleeding events**

Forty-two of 61 (68.9%) subjects who were on prophylaxis regimens for all or part of their treatment and 10 of 12 (83.3%) 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 1 and 2). However, some of the bleeding episodes reported in 2009 were not rated due to misunderstanding between the applicant and the contract research organization.

Table 1. Bleeding efficacy*

Characteristics	Prophylaxis (1) N=61 n (%)	On Demand (1) N=12 n (%)	Total N=65 n (%)
Number of Subjects with Bleeds	42(68.9)	10(83.3)	47(72.3)
Number of Bleeds	303	227	530
Subject Rating of Efficacy			
Not Rated (2)	62(20.5)	37(16.3)	99(18.7)
Rated	241(79.5)	190(83.7)	431(81.3)
Excellent	123(51.0)	54(28.4)	177(41.1)
Good	78(32.4)	107(56.3)	185(42.9)
Fair	30(12.4)	26(13.7)	56(13.0)
Poor	10(4.1)	3(1.6)	13(3.0)

*Source: applicant's summary using program EF_AL_T07.sas from file "ib1001-01-report-body.pdf".

Table 2. Infusions required to stop bleed

	Prophylaxis at time of bleed		On-demand at time of bleed	
Number of infusions/bleed	Frequency	Percent (%) of all bleeds*	Frequency	Percent (%) of all bleeds
1	191	66.78	172	75.77
2	49	17.13	25	11.01
3	15	5.24	17	7.49
4	10	3.50	8	3.52
5	8	2.80	1	0.44
6	3	1.05	2	0.88
7	2	0.70	0	0.0
8	2	0.70	1	0.44
9	2	0.70	0	0.0
11	2	0.70	0	0.0
19	1	0.35	0	0.0
20	1	0.35	0	0.0
24	0	0.0	1	0.44
Total	286	100	227	100

*The number of infusions to stop the bleed was not reported for all bleeds during the prophylaxis treatment.

Over the surveillance period (39 months) for the prophylaxis arm, investigators rated treatment effectiveness every three months. The regimen was consistently rated as effective by the investigators, with very few exceptions where the rating was “partially effective”. None of the ratings were reported “not effective” or “not applicable”.

- **Annualized bleeding rates (ABR)**

The total time (in years) for the subjects on the prophylaxis and on-demand treatment regimen is summarized in Table 3 below. More than 90% of subjects had total prophylaxis treatment duration > 6 months, 74% of them had total prophylaxis treatment duration > 1 year. The mean on-demand treatment duration is shorter: 58% of subjects had total on-demand treatment duration > 1 year.

Table 3. Total time on treatment (in years)

Treatment regimen	**N**	**Mean**	**Std Dev**	**Min**	**Max**
Prophylaxis	61	1.49	0.78	0.21	3.30
On-demand	12	1.24	0.79	0.23	2.52

A statistically significant difference in the mean ABR (after square-root transformation) between subjects receiving prophylaxis and those treated on-demand was observed, as reported in Table 4 below. The p-value is <0.001.

Table 4. ABR after square-root transformation*

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

*Source: applicant's Table 11:12 from file "ib1001-01-report-body.pdf".

ABR on the original scale for each treatment regimen is presented in Table 5 below. Because the data is not normally distributed, non-parametric descriptive statistics are reported. The median ABR is 1.52 vs. 16.39 for the prophylaxis vs. on-demand treatment regimens.

Table 5. ABR: ITT population

Treatment regimen	Prophylaxis	On-demand
n	61	12
Min	0	0
25^{th} percentile	0	6.60
Median	1.52	16.39
75^{th} percentile	3.46	23.71
Max	47.52	39.43

The distribution of ABR on the original scale for the prophylaxis regimen is extremely right skewed, as shown in the histogram in Figure 1. On the contrary, the distribution ABR for the on-demand regime is relatively uniform across the range, see Figure 2.

Figure 1: ABR of prophylaxis regimen

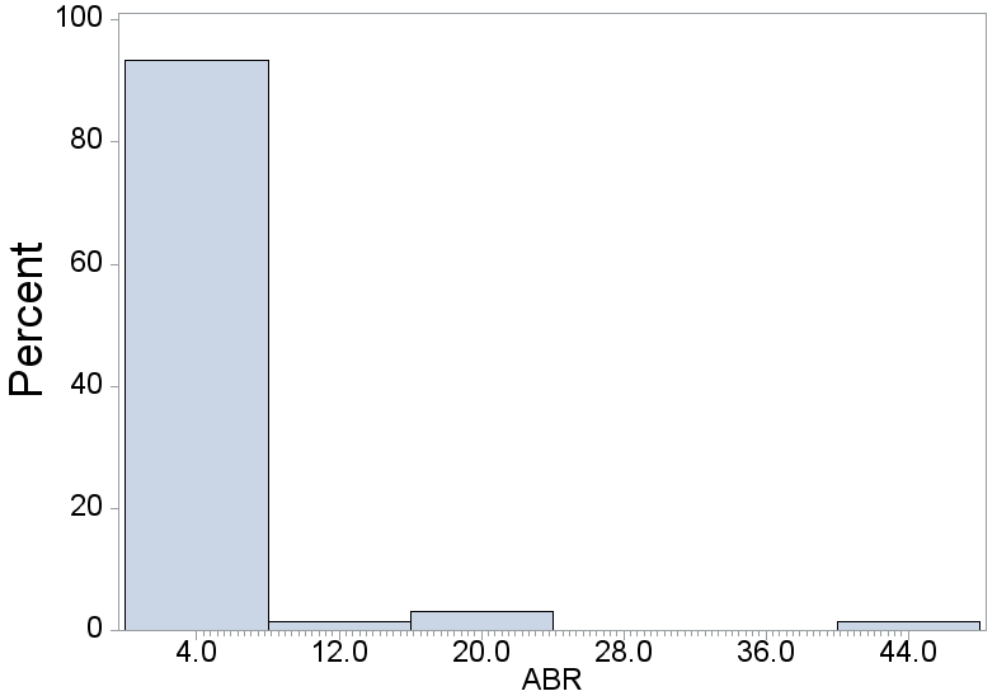
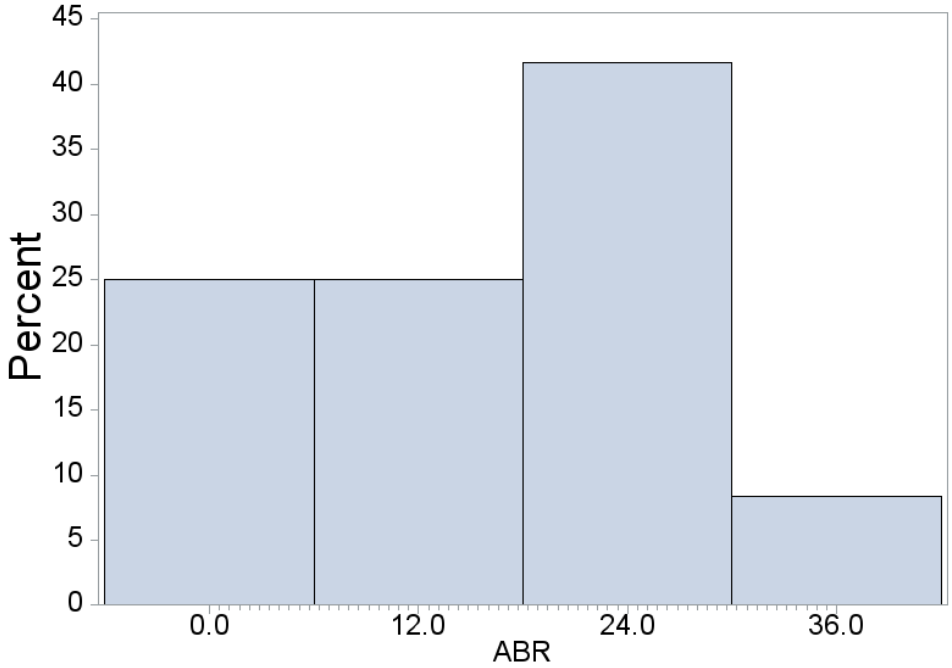


Figure 2: ABR of on-demand regimen



The applicant compared the ABR on the original scale by cause for the two treatment regimens in Table 6. A higher percentage of trauma-related bleeding episodes were reported when subjects were on prophylaxis than when the subjects were treated on-demand. On the other hand, most of the bleeding episodes from subjects treated on-demand were spontaneous.

Table 6. ABR by cause*

	Prophylaxis			On-Demand		
	Trauma	**Spontaneous**	**Unknown**	**Trauma**	**Spontaneous**	**Unknown**
n	61	61	61	12	12	12
Minimum	0.00	0.00	0.00	0.00	0.00	0.00
25th percentile	0.00	0.00	0.00	0.00	1.89	0.00
Median	0.00	0.00	0.00	2.67	7.49	0.00
75th percentile	2.43	1.22	0.63	3.96	21.32	1.44
Maximum	43.61	23.82	2.99	7.09	39.66	11.99

*Source: applicant's Table 11:17 from file "ib1001-01-report-body.pdf".

6. Comments to the review committee:

1) Four subjects in the prophylaxis group had an ABR >10 on the original scale. Their ID and detailed data are listed in the Table 7 below. Subject (b) (6)) withdrew because of a perceived lack of efficacy. Although the study won the primary efficacy endpoint based on the mean ABR, please evaluate whether it is acceptable to have such unfavorable results from the four individuals for the consideration of product approval, or whether these data should be included in the labeling.

Table 7. ABR >10 subjects on prophylaxis

ID	Age (years)	Time on prophylaxis (years)	# of bleeds			ABR
			Trauma	Spontaneous	Unknown	
(b) (6)	18+	0.7	32	2	1	47.5
(b) (6)	18+	0.4	0	9	0	23.6
(b) (6)	12 - <18	1.2	17	3	3	18.7
(b) (6)	18+	1.7	14	9	2	14.6

7. Communication with the applicant:

The following two comments based on the mid-cycle review were sent to the applicant via an email Information Request on May 22, 2014. The applicant's responses received on May 29 in amendment 125426/0/29 are summarized under each comment.

1) Reporting the square-root transformed annualized bleeding rate could be misleading, although it may be acceptable to normalize the data by transformation during the statistical analysis. Please update your study report on annualized bleeding rate based on the original scale.

Response:

- The square-root transformed method of calculating the ABR in clinical study IB1001-01 was defined in the original protocol. As a result, square-root transformed ABR was part of a pre-planned statistical analysis.
- Since the ABR follows a Poisson distribution and strongly skews to the right with a large range, using the mean and standard deviation under original scale to describe the ABR distribution may not be a best representation of the data.
- Calculating the ABR with transformation is consistent with what has been previously reported for other factor concentrates (ADVATE [Antihemophilic Factor (Recombinant)].
- Regardless, both the square-root transformed ABR and the ad hoc analysis assessing the original scale ABR (total ABR; the median and the range) have been presented in the Consolidated Clinical Study Report (CSR) for study IB1001-01.
- For the reasons above, an update to the CSR is not planned at this time.

Reviewer Comment:

- *In the CSR, one table of ABRs based on the original scale was included among many tables in Section 14: Tables, Figures and Graphs Referred to but not included in the text. In the main text, most of the ABRs reported were square-root-transformed, sometimes without such indication.*
- *Only results based on square-root transformed data are reported in the label. The clinical reviewer strongly disagrees with this approach.*

2) On page 100 of the clinical study report, it is stated that "In the prophylaxis treatment group, 42 subjects (68.9%) experienced a total of 286 bleeding episodes…" However, the summary table generated by program "EF_AL_T07.sas" indicates that the total number of bleeding episodes is 303. Please correct this inconsistency.

Response:

Table EF_AL_T07 refers to the total number of "bleeding events", not "bleeding episodes". An episode may have consisted of more than one bleeding event, consistent with standard practice.

Reviewer Comment: *acceptable*

Comment to the applicant to be included in the second CR letter:

We have reviewed your response dated May 29, 2014 to the two statistical items in the FDA Information Request dated May 22, 2014. Your response to the second item is acceptable.

Your response to the first item is not acceptable. Data transformation is an acceptable approach to compare two treatment regimens/groups for non-normalized data, however reporting the square-root-transformed ABR may cause confusion. Although that same data transformation was used in the statistical analysis in the ADVATE licensing application, only results based on data on the original scale are reported in the package insert of ADVATE. Therefore, please

1) Update the CSR with at least one table of ABR based on the original scale in sections 11.4.1.2.1.1 and 11.4.1.2.1.3 respectively.
2) Clearly indicate in the CSR when transformed ABRs are reported.
3) Revise the label to report ABR based on the original scale only, and use non-parametric statistics if needed.

8. Conclusions and recommendation:

1) In response to FDA's two statistical items in the CR letter dated February 1, 2013, ABRs have been recalculated using a more current data cut-off and a revised annualized bleeding rate definition. The response is acceptable.
2) The updated results of ABR are now reproducible. A statistically significant difference in the mean ABR (after square-root transformation) between subjects receiving prophylaxis and those treated on-demand was observed.
3) FDA requested the applicant to report the ABR based on the original scale, instead of the square-root transformed scale. The applicant does not agree and argues that it is a pre-specified analysis. A further comment will be sent out to reiterate that data transformation may be acceptable in statistical analysis, but the final reporting should be based on the original scale to avoid misunderstanding, especially in the label.
4) A second CR decision was made based on the review of other disciplines, and the above comment will be included in the CR letter.

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