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Applicant	CSL Behring Recombinant Facility AG
(Proposed) Trade Name	IDELVION™
Indication(s) and Intended Population(s)	Indicated in all patients (adult and pediatric) with hemophilia B for <ul style="list-style-type: none"> <li>• Routine prophylaxis to prevent or reduce the frequency of bleeding episodes,</li> <li>• On-demand treatment and control of bleeding episodes,</li> <li>• Perioperative management of bleeding</li> </ul>

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## GLOSSARY

### Abbreviation Definition

ABR	Annualized bleeding rate
AE	Adverse event
AsBR	Annualized spontaneous bleeding rate
CI	Confidence interval
Cmax	Maximum concentration
ED	Exposure day(s)
FIX	Factor IX
ISE	Integrated summary of efficacy
IV	Intravenous
PK	Pharmacokinetic(s)
PP	Per Protocol
rFIX	Recombinant factor IX
rIX-FP	Recombinant fusion protein linking coagulation factor IX with albumin
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation

## 1. EXECUTIVE SUMMARY

The product rIX-FP was developed to treat patients with Hemophilia B. The pivotal study (3001) was a prospective, open-label, multi-center study of 63 previously treated male subjects 12 to 65 years of age. The Primary Efficacy population consisted of 19 subjects who started with on-demand treatment then switched to weekly prophylaxis treatment. The primary efficacy endpoint, annualized spontaneous bleeding rate (AsBR) of the two treatment regimens was compared on these 19 subjects, and more than 50% reduction of AsBR was demonstrated after switching. The median AsBR was 15.43 for on-demand treatment and 0.71 for the prophylaxis treatment. In the Efficacy population based on all 63 subjects, most of the bleeding episodes (353/358, 98.6%) were treated successfully with 1 or 2 infusions of rIX-FP. The investigators reported that the rIX-FP treatment was effective (excellent or good) for 94.1% (337/358) of the bleeding episodes.

There were 15 surgeries from all clinical studies (pivotal or non-pivotal) in the rIX-FP clinical development program. Hemostatic efficacy was rated excellent or good for all surgeries by the investigators.

There have been no reports of inhibitors to factor IX in the 111 previously treated subjects in all clinical studies. One previously untreated subject from the ongoing study (3003) reported a low titer inhibitor against factor IX. Study 3003 is still enrolling previously untreated subjects and to date very few have been enrolled.

The overall efficacy and safety are acceptable.

In the pivotal study, the prophylaxis efficacy of a weekly interval was compared to an extended interval (10-day or 14-day) based on 26 subjects in the prophylaxis arm who switched from weekly to an extended prophylaxis interval. The mean AsBR was 0.23 for the weekly treatment regimen and 0.85 for the extended treatment regimens with a mean difference of -0.62 (95% CI: -1.41, 0.16) which met the pre-specified non-inferiority

margin of -6. However, these 26 subjects had less frequent bleeding during weekly prophylaxis compared to the other 12 subjects who did not switch. If the extended prophylaxis interval indication (10-day and/or 14-day) is approved, we recommend that the labeling reflect the fact that the results were based on a subgroup of subjects who met pre-specified switching criteria, and may not be generalizable to the Hemophilia B population at large.

There are no remaining statistical issues.

## 2. CLINICAL AND REGULATORY BACKGROUND

Hemophilia B is an X-linked recessive inherited bleeding disorder, which affects 1 in 50,000 males. Hemophilia B results from a deficiency of coagulation factor IX (FIX), a protein that is essential to the blood coagulation. The first recombinant FIX (rFIX) product (BeneFIX<sup>TM</sup>) was approved in 1997. The half-life of FIX requires prophylaxis treatment 2 to 3 times a week to achieve a significant reduction of bleeding episodes.

This applicant developed recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP), which uses the albumin fusion technology to extend the half-life of FIX. This new product has not been approved in any country. The FDA Office of Orphan Product Development has granted rIX-FP orphan drug designation.

The proposed indication for rIX-FP below is supported by data from five studies (three non-IND studies and two studies under IND 14978):

- routine prophylaxis to prevent or reduce the frequency of bleeding episodes,
- on-demand treatment and control of bleeding episodes,
- perioperative management of bleeding.

The format and content of this submission were in accordance to the agreements made during the pre-BLA meeting on May 19, 2014. Based on the agreement, the Integrated Summary of Efficacy (ISE) was formatted in accordance with FDA Guidance for Industry, Integrated Summaries of Effectiveness and Safety: Location within the common technical document, April 2009, Example 4: Small ISE Split between Module 2 and Module 5. Text and major data presentations are located in Module 2.7.3 while source data are located in Module 5.3.5.3 (ISE) and Module 5.3.3.2 (individual clinical study reports). As promised, the applicant provided a safety update 4 months after the BLA submission.

## 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

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

### 5.1 Review Strategy

The main focus of this review is Study 3001, to be covered in Section 6.1. Study 3003 is the extension of Study 3001 and will be briefly covered in Section 6.2. Only these two studies were conducted under IND 14978.

Study 3002 (Phase 3 pediatric) will be briefly covered in Section 6.3.

The ISE will be reviewed in Section 7 based on data from studies 2004, 3001, 3002 and 3003. Integrated results from studies 2004 and 3001 will be included in Section 7.1 (routine prophylaxis) and Section 7.2 (on-demand treatment and control of bleeding). The data for perioperative hemostasis derive from studies 3001, 3002 and 3003 and will be covered in Section 7.3. Although study 2004 was also designed to provide data for this indication, none of the subjects underwent elective surgery.

Study 2001 will not be reviewed.

I defer to the clinical reviewer for the evaluation of integrated summary of safety (ISS) and to the Pharmacokinetic (PK) reviewer for the evaluation of all PK studies.

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

The following documents were submitted under BLA 125582/0. At the time of the original submission, Studies 3002 and 3003 were not completed and the data cut-off date was July 15, 2014.

- Module 1.6.3 FDA Meeting Minutes (June 17, 2014)
- Module 2.5 Clinical Overview
- Module 2.7.3 Summary of Clinical Efficacy
- Module 5.3.5.2 Study 3001 Study Report Body
- Module 5.3.5.2 Study 3001 Study Analysis Plan
- Module 5.3.5.2 Study 3002 Study Report Body
- Module 5.3.5.3 ISE

On April 3, 2015, the applicant submitted a 4-month safety update under BLA 125582/0/8. At the time of this amendment, Study 3002 was completed and Study 3003 was ongoing with a data cut-off date of January 9, 2015. The following materials from the amendment are covered in this review:

- Module 2.7.3 Summary of Clinical Efficacy
- Module 5.3.5.2 CSL654\_3001 Clinical Study Report Addendum
- Module 5.3.5.2 CSL654\_3003 Abbreviated Clinical Study Report

### 5.3 Table of Studies/Clinical Trials

The clinical program comprised five studies, presented in Table 1.

**Table 1.** Overview of rIX-FP Clinical Studies

Study number	Study design	Primary objective	Population age: mean (range)	Study status
Study 2001	Phase 1, prospective, MC, OL, dose-escalation	Safety and laboratory changes	25 male subjects with Hemophilia B, 35 (15-58) years	Completed
Study 2004	Phase 1/2, prospective, MC, OL	Safety, laboratory changes, inhibitor formation and antibody development	17 male subjects with Hemophilia B, 26 (13-46) years	Completed
Study 3001	Phase 2/3, prospective, MC, OL, (pivotal)	<u>Main study:</u> Efficacy in preventing bleeding episodes and inhibitor development <u>Surgery substudy:</u> efficacy	63 male subjects with Hemophilia B, 33 (12-61) years	Completed
Study 3002	Phase 3, prospective, MC, OL, (pediatric)	PK and inhibitor development	27 male subjects with Hemophilia B, 5.9 (1-10) years	Completed
Study 3003	Phase 3b, prospective, MC, OL, (extension)	<u>Main study:</u> inhibitor development <u>Surgery substudy:</u> efficacy	81 male subjects with Hemophilia B; 27.5 (2-63) years <sup>a</sup>	Ongoing

<sup>a</sup>: For the Safety Population (N=80)

Abbreviations: MC Multicenter; OL Open-label

Source: Original BLA 125582/0/8; Summary of Clinical Efficacy, Table 1–2, p.8

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

### 6.1 Study 3001

When Study 3001 was completed on November 7, 2014 there were 6 subjects in the Primary Efficacy population that completed the study with at least 12 weeks, but less than 26 weeks, of prophylaxis treatment. Of these 6 subjects, 3 continued with their weekly prophylaxis regimen in Study 3003 and remained on the same regimen until completing at least 26 weeks on prophylaxis. The results of ABR and AsBR in this review were based on an extended data set that includes data from the 3 subjects in Study 3003. All other parameters were analyzed on the original data sets without the additional data from these 3 subjects.

#### 6.1.1 Objectives

The primary objectives were to evaluate the efficacy of rIX-FP in routine prophylaxis to prevent or reduce the frequency of bleeding episodes and safety of rIX-FP with respect to

the development of inhibitors against FIX in subjects with severe Hemophilia B (FIX activity of  $\leq 2\%$ ).

Some of the important secondary objectives were:

- To evaluate the clinical response to rIX-FP for the on-demand treatment and control of bleeding episodes in subjects with severe hemophilia B
- To evaluate the safety of rIX-FP, based on AEs and the development of antibodies to rIXFP
- To evaluate the efficacy of rIX-FP in perioperative management of bleeding episodes (primary objective of the surgical substudy)

#### 6.1.2 Design Overview

This was a prospective, open-label study. Approximately 60 previously treated subjects were planned to be enrolled. After a 1-month screening period and up to a 14-day PK period, subjects would be assigned to either prophylaxis (Arm 1) or on-demand (Arm 2) based on their history of use with FIX products (i.e., prophylaxis or on-demand).

- Approximately 35 subjects were to be enrolled in Arm 1 to receive 7-day prophylaxis for  $\geq 26$  weeks (if coming from Study 2004) or  $\geq 30$  weeks otherwise. After completing the required 7-day prophylaxis, subjects could switch to a 10-day or 14-day treatment interval for 30 weeks provided the subject met all the following switching criteria as determined by the investigators:
  - Be on a stable dose in the previous month (no dose adjustment).
  - Not have experienced spontaneous bleeding event in the previous month.
  - Currently on a weekly prophylaxis dose of  $\leq 50$  IU/kg rIX-FP.
  - Be willing to switch to a longer treatment interval.

If a subject was receiving a dose of  $\leq 40$  IU/kg during rIX-FP weekly treatment, the new treatment interval would be 14 days. If the dose was 40-50 IU/kg, the new treatment interval would be 10 days.

- Approximately 25 subjects were to be enrolled in Arm 2, to receive approximately 26 weeks of on-demand treatment, followed by approximately 26 weeks (minimum of 12 weeks) of weekly prophylaxis therapy with rIX-FP. The primary efficacy analysis was conducted only on the subjects who switched from the on-demand treatment to weekly prophylaxis.

During the active treatment periods, subjects recorded the infusion information and treatment response via the subject electronic diary. Efficacy and safety assessments were performed at the study site on a monthly basis.

Any subjects requiring nonemergency surgery during the course of the study could be enrolled in the surgical sub-study, with a target enrollment of at least 5 subjects undergoing 10 major surgeries.

### 6.1.3 Population

This study included male subjects, 12 to 65 years of age, with severe Hemophilia B. Subjects in the on-demand arm should be willing to switch to a prophylaxis regimen.

### 6.1.4 Study Treatments or Agents Mandated by the Protocol

The treatment arms and assigned doses are shown in Table 2.

**Table 2.** Treatment Groups and Assigned Doses

Treatment arms	Prophylaxis dose			On-Demand dose
	7-day interval	10-day interval	14-day interval	
Arm 1 (prophylaxis)	35-50 IU/kg Max 75 IU/kg	75 IU/kg	75 IU/kg	35-50 IU/kg Max 75 IU/kg
Arm 2 (on-demand)	35-50 IU/kg Max 75 IU/kg	--	--	35-50 IU/kg Max 75 IU/kg

Abbreviations: Max maximum.

Source: Original BLA 125582/0; CSL654\_3001 Study Report Body, Table 9–1, p.33

### 6.1.6 Sites and Centers

Subjects were enrolled from 32 sites in 10 countries, 4 geographic regions: Asia (Japan), Europe, Middle East (Israel), and North America (US).

### 6.1.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint was the annualized spontaneous bleeding rate (AsBR) for bleeding episodes requiring treatment during on-demand treatment compared with that during routine prophylaxis treatment for subjects in Arm 2. A bleeding episode starts with the first sign of a bleed, and ends 72 hours after the last treatment for the bleed; within which any symptoms of bleeding at the same location, of the same type, or infusions less than 72 hours apart, are considered the same bleed. A bleeding episode at a different location will be considered a separate bleed regardless of the time from the last infusion.

AsBR was derived for each subject as follows: (number of spontaneous bleeding episodes) / (observed treatment period of interest) \* 365.25. The treatment period began with the administration of the first weekly dose of rIX-FP, and ended 7 days after the final weekly prophylaxis dose, or at the administration of the first extended interval regimen; or at the end of study visit; whichever occurred first.

The primary safety endpoint of the study was formation of inhibitors to FIX. Inhibitor formation was defined as any inhibitor ( $\geq 0.6$  BU/mL) identified and confirmed by retesting. For estimating the incidence, the numerator included all subjects with inhibitors regardless of Exposure Days (EDs) to rIX-FP and the denominator included subjects with at least 50 EDs plus subjects with <50 EDs but with inhibitors. An ED of rIX-FP was defined as any day that the subjects receive an infusion of rIX-FP. Success was achieved if the upper confidence limit of the two-sided 95% CI was less than the acceptable upper limit of 10.65%.

The secondary endpoints of the study included:

- Annualized bleeding rate (ABR) for total bleeding episodes in Arm 2
- Investigator's overall clinical assessment of hemostatic efficacy for treatment of bleeding episodes, based on a four point ordinal scales (minor/moderate bleeding episodes: excellent, good, moderate, and none; major bleeding episodes: excellent, good, moderate and poor/no response).
- Investigator's (or surgeon's) overall clinical assessment of hemostatic efficacy for surgical prophylaxis, based on a four point ordinal scale (excellent, good, moderate, poor/ none).
- Occurrence of related adverse events (AEs) to rIX-FP over the course of the study
- Occurrence of antibodies against rIX-FP
- Number of infusions to achieve hemostasis. The treatment outcome was considered a success if 1 or 2 infusions were required to achieve hemostasis. To be considered clinically relevant, one would expect to observe that 85% of bleeding episodes were treated with 1 or 2 infusions. As an acceptance criterion, the lower limit of the 2-sided 95% CI should exceed 80%.
- rIX-FP consumed per month while maintaining assigned prophylaxis regimen
- AsBR among Arm 1 subjects who switched regimens

#### 6.1.9 Statistical Considerations & Statistical Analysis Plan

##### Sample size justification

- Arm 1(prophylaxis): approximately 35 subjects were to be enrolled in order to enroll a total of at least 50 subjects overall in the study (both arms) to meet the criterion of no more than 1 inhibitor in 50 subjects.
- Arm 2 (on-demand): approximately 25 subjects were to be enrolled to target 21 evaluable subjects for the primary efficacy analysis. The null and alternative hypotheses, where  $\mu_{\text{prophylaxis}}$  and  $\mu_{\text{on-demand}}$  are the mean AsBR with prophylaxis and on-demand treatments, respectively, are as follows:

$$H_0: \mu_{\text{prophylaxis}} / \mu_{\text{on-demand}} \geq 0.50 \text{ versus } H_A: \mu_{\text{prophylaxis}} / \mu_{\text{on-demand}} < 0.50$$

The sample size was estimated under the following assumptions: a one-sided type I error rate of 0.025 and 95% power for a matched-pair design where the correlation of measurements on the same subjects is 0.50, the coefficient of variation is between 1.0 and 1.6, and the ratio  $\mu_{\text{prophylaxis}}/\mu_{\text{on-demand}}$  under the alternative hypothesis is between 0.20 and 0.40.

*Reviewer's comment: during the IND stage, upon FDA's request, the applicant amended the sample size calculation several times to reflect wanting to demonstrate more than a 50% reduction of AsBR. The above sample size justification is still questionable: 1) the hypotheses are not written for paired data, and 2) the calculation uses a parametric approach, rather than the non-parametric Wilcoxon signed-rank test, which is the primary analysis method. The applicant acknowledged that the power may be slightly lower with the nonparametric test.*

### Definition of analysis populations

- Safety population: all subjects who received at least 1 dose (or partial dose) of rIX-FP during the study. This population was used for all safety analyses and assessment of antibody development.
- Efficacy population: all subjects who received at least 1 dose of rIX-FP as part of either routine prophylaxis treatment or on-demand treatment during the study. This population was used for the analysis of all secondary efficacy endpoints except as noted for the Primary Efficacy population.
- Primary Efficacy population: all subjects in the Efficacy population assigned to the on-demand treatment arm (Arm 2) who received at least 1 dose of on-demand treatment and also received at least 1 dose of routine prophylaxis treatment. This population was used for the analysis for the primary efficacy endpoint and one secondary efficacy endpoint: ABR for total bleeding episodes in Arm 2.
- Per Protocol (PP) population: all subjects in the Efficacy population who did not have any inclusion or exclusion criteria deviations and who incurred no protocol deviations that pertained to the assessment of treatment efficacy. This population was used for supporting analyses for the secondary efficacy endpoints.
- Surgical population: all subjects who received at least 1 dose of rIX-FP for a major or minor surgical procedure. This population was used for all perioperative analyses.

### Primary efficacy analysis (AsBR in Arm 2)

The AsBR was analyzed using the Wilcoxon signed-rank test. A test of the null hypothesis that the median ratio of AsBR (prophylaxis/on-demand) was  $\geq 0.50$  was conducted at the 1-sided 0.025 level. The ratio was based on the original scale.

If a subject completed at least 12 weeks of treatment, the AsBR was estimated using the subject's observed data for that treatment period. However, if a subject had at least 12 bleeding episodes with on-demand treatment, then the observed data was used regardless of the observation time. Otherwise, the AsBR was considered missing and to be handled as follows:

- Missing on-demand AsBR was imputed using the mean observed among on-demand subjects who had at least 12 weeks of treatment or had at least 12 bleeding episodes during the on-demand treatment period.
- Missing prophylaxis AsBR was imputed according to the reason for withdrawal. If the reason for withdrawal was not for lack of efficacy, then the mean observed AsBR with prophylaxis treatment was used. If the reason for withdrawal was lack of efficacy, then the highest observed AsBR with prophylaxis treatment was used.

### Sensitivity analyses

To evaluate the robustness of the results against assumptions regarding missing data during the prophylaxis treatment period, three sensitivity analyses were conducted using sensitivity analysis datasets as described below:

- Any missing prophylaxis AsBR were imputed using the mean observed AsBR with prophylaxis treatment (sensitivity analysis dataset 1)
- Any missing prophylaxis AsBR were imputed using the highest observed AsBR with prophylaxis treatment (sensitivity analysis dataset 2)
- Any missing prophylaxis AsBR were imputed using the subjects on-demand AsBR (sensitivity analysis dataset 3)

#### Primary safety analysis

A 2-sided 95% Exact CI for the incidence of inhibitor formation was calculated.

#### Additional analysis of primary efficacy endpoint / secondary endpoints

- AsBR (additional analysis)

A Poisson distribution (SAS (b) (4) approach, with the repeated option for the paired data, was used to analyze the AsBR to take into account the potential impact of differential follow-up.

- ABR for total bleeding episodes in Arm 2

The primary efficacy analysis and above Poisson model were repeated for the total treated bleeding episodes, regardless of the bleeding cause.

- Number of infusions of rIX-FP to achieve hemostasis in the treatment of minor/moderate bleeding episodes

The number and percentage of minor/moderate treated bleeding episodes requiring 1, 2, or >2 infusions of rIX-FP treatment to achieve hemostasis were tabulated. To account for within-subject correlation, a generalized linear model (containing only the intercept term) using SAS (b) (4) procedure with a log link function was utilized.

- Investigator's overall clinical assessment of hemostatic efficacy for the treatment of bleeding episodes

This analysis was performed separately for minor/moderate bleeding episodes and major bleeding episodes. The proportion of bleeding episodes whose treatment was assessed as effective (excellent or good) by the investigators would be provided.

- rIX-FP consumption during routine prophylaxis

The consumption of rIX-FP was summarized using descriptive statistics. In addition, summaries are provided according to geographic location.

- Comparison of AsBR between the 7-day and >7-day prophylaxis regimens

The AsBR of 7-day prophylaxis regimen was compared with the 10-day or 14-day prophylaxis regimens (i.e., extended), on Arm 1 of the Efficacy population. A non-inferiority approach was taken to compare the mean AsBR ( $\mu_{7\text{-day}}$  and  $\mu_{\text{extended}}$ ). The lower confidence limit of the 95% CI, based on a 1-sample (paired) t-test for the difference between the two means, must be greater than -6.

$$H_0: \mu_{7\text{-day}} - \mu_{\text{extended}} \leq -6$$

$$H_1: \mu_{7\text{-day}} - \mu_{\text{extended}} > -6$$

This analysis only included subjects who were treated with both the 7-day prophylaxis regimen and an extended prophylaxis regimen (every 10 or 14 days) for at least 12 weeks.

- Occurrence of related adverse events (AEs) to rIX-FP over the course of the study  
Descriptive analyses were used.

- Occurrence of antibodies against rIX-FP

Descriptive analyses were used.

- Investigator’s assessment of hemostatic efficacy for surgical prophylaxis

The proportion of bleeding episodes whose treatment was assessed as effective by the investigators would be provided.

### Changes in SAP

In amendment 3 dated February 27, 2014, the bleeding episodes that occurred during the 4-week run-in period of prophylaxis therapy for subjects in Arm 2 (on-demand) were no longer to be excluded from analyses of the 26-week treatment period, and the total duration of treatment for Arm 2 was reduced from 30 weeks to 26 weeks, but a minimum of 12 weeks.

### 6.1.10 Study Population and Disposition

#### 6.1.10.1 Populations Enrolled/Analyzed

The number of subjects included in each analysis population is summarized in Table 3. The Safety and Efficacy populations are identical.

**Table 3.** Analysis Populations

Analysis population	Number of subjects		
	Propylaxis (Arm 1) (N=40)	On-demand (Arm 2) (N=23)	Overall (N=63)
Safety	40	23	63
Efficacy	40	23	63
Primary efficacy	0	19	19
PP	40	21	61
Surgical	3	1	4

Source: Original BLA 125582/0; CSL654\_3001 Study Report Body, Table 11–1, p.73

#### 6.1.10.1.1 Demographics

The majority of subjects were white (52/63 subjects, 82.5%) and non-Hispanic (62/63 subjects, 98.4%). The distribution of race and ethnicity were similar in both arms. All the

11 subjects enrolled from the Middle East were in the prophylaxis treatment arm. The mean age for the overall population was 33.0 years (range, 12 to 61 years). All seven adolescent subjects (12 to <18 years of age) were enrolled from Europe and the Middle East, and were all in Arm 1 (prophylaxis). The distribution of age, race and region is presented in Table 4.

**Table 4. Age, Race, and Region (Efficacy Population)**

Age	Race	Region			
		Asia	Europe	Middle East	North America
12-18 years old	White	0	5	2	0
≥18 years old	Asian	10	0	0	0
	Black	0	0	0	1
	White	0	31	9	5

#### 6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All subjects had been diagnosed with Hemophilia B and had a FIX activity level  $\leq 2\%$ . The time since diagnosis was similar between the two treatment arms.

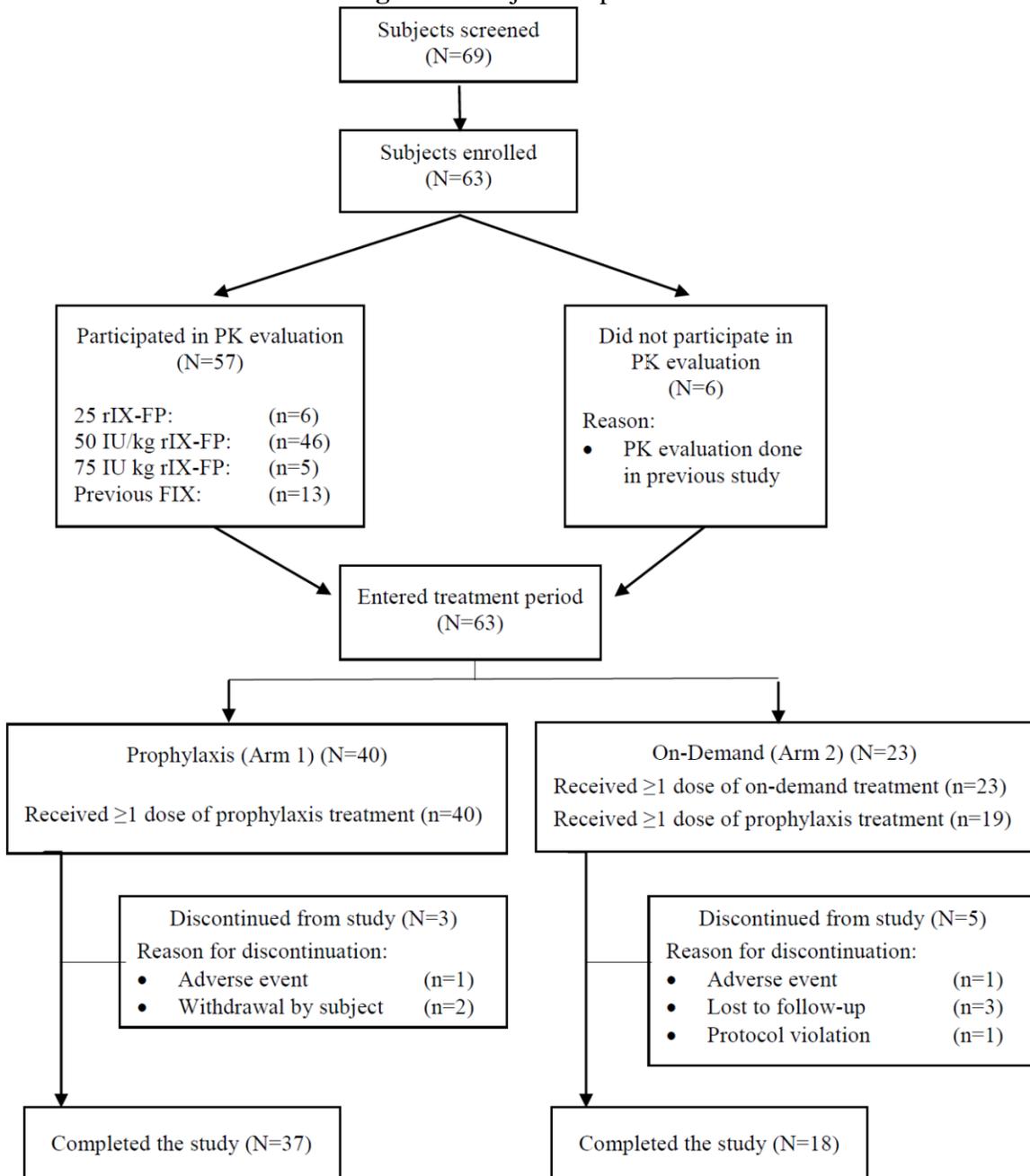
The majority (34/40) of subjects in the prophylaxis treatment arm received previous FIX as routine prophylaxis treatment. On the contrary, the majority (17/23) of subjects in the on-demand treatment arm received previous FIX for on-demand treatment; 5/23 subjects reported treatment prior to activity for the prevention of bleeding and no subject received previous FIX for routine prophylaxis.

In the 12 months prior to study entry, subjects in the prophylaxis treatment arm experienced much fewer bleeding episodes than subjects in the on-demand treatment arm. For example, the mean total bleeding episodes in last 12 months was 3.4 and 24.3 for prophylaxis and on-demand, respectively.

#### 6.1.10.1.3 Subject Disposition

Subject disposition is illustrated in Figure 1. Overall, 55/63 (87.3%) subjects completed the study (37/40 [92.5%] in the prophylaxis treatment group and 18/23 [78.3%] in the on-demand treatment group).

**Figure 1. Subject Disposition**



Source: Original BLA 125582/0; CSL654\_3001 Study Report Body, Figure 10-1, p.70

### 6.1.11 Efficacy Analyses

#### 6.1.11.1 Analyses of Primary Endpoint

The median (Q1, Q3) duration of treatment for the 19 subjects in the Primary Efficacy analysis set was 187.0 (183.0, 192.0) days in the on-demand treatment arm and 316.0 (121.0, 518.0) days in the prophylaxis treatment arm. The AsBR was significantly reduced when subjects switched from on-demand to weekly prophylaxis treatment with

rIX-FP (see Table 5). The p-value was <0.0001 based on a Wilcoxon signed-rank test of AsBR ratio (prophylaxis/on-demand)  $\geq 0.50$ . All subjects experienced at least two spontaneous bleeding episodes during the on-demand regimen while 11 subjects did not have any spontaneous bleeding episodes during the prophylaxis regimen.

**Table 5.** AsBR (Primary Efficacy Population)

	On-demand regimen (N=19)	Prophylaxis regimen (N=19)
Annualized spontaneous bleeding rate (bleeding episodes/year/subject)		
N	19	19
Mean (SD)	14.57 (8.421)	0.90 (1.171)
Median	15.43	0.71
Q1, Q3	7.98, 17.96	0.00, 1.58
Min, Max	2.0, 39.5	0.0, 4.2

Source: Original BLA 125582/0/8; CSL654\_3001 Clinical Study Report Addendum,, Table 11–1, p.15

Subject (b) (6) was lost to follow-up after completing only 12 days on prophylaxis treatment; therefore the AsBR for this subject was imputed using the mean observed AsBR with prophylaxis treatment. All sensitivity analyses supported the robustness of the primary results.

#### 6.1.11.2 Additional analysis of primary efficacy endpoint / secondary efficacy endpoints

- AsBR (additional analysis)

The Poisson model yielded similar results as the primary analysis.

- Annualized bleeding rate (ABR) for total bleeding episodes in Arm 2

During routine prophylaxis, the median (Q1, Q3) ABR was 1.58 (0.00, 4.30), while during on-demand treatment, the median ABR was 19.22 (16.70, 25.84).

- Number of infusions of rIX-FP to achieve hemostasis in the treatment of minor/moderate bleeding episodes

A total 358 bleeding episodes required treatment and all of them were minor in severity. Of these, 353 bleeding episodes (98.6% with 95% CI: 96.2% to 99.5% based on the applicant’s analysis) were treated successfully with 1 or 2 infusions, with the lower bound exceeding the pre-specified success criterion of 80%. The 5 bleeding episodes that required >2 infusions to achieve hemostasis occurred on 4 subjects in the on-demand treatment arm. The maximum number of infusions required to achieve hemostasis was 5.

*Reviewer’s comment: although I am not able to replicate the above CI using any statistical method that I am aware of, I determined that there is no need to ask for clarification because 1) the lower bound of the applicant’s method is only slightly different from the lower bound generated by any of these methods; and 2) the applicant’s method yields a more conservative value: a smaller lower bound than any of these methods does.*

- Investigator’s overall clinical assessment of hemostatic efficacy for the treatment of bleeding episodes

The analysis was conducted on the above same 358 bleeding episodes. The investigators reported that the rIX-FP treatment was effective (excellent or good) for most bleeding episodes (337/358=94.1%), as presented in Table 6. The 11 missing data points were treated as non-effective in the calculation.

**Table 6.** Investigator’s Assessment of Hemostatic Efficacy (Efficacy Population)

Bleeding Severity Assessment	Prophylaxis (Arm 1) (N=40) n (%)	On-demand (Arm 2) (N=23) n (%)	Total (N=63) n (%)
Minor/moderate bleeding episodes			
Number of bleeding episodes requiring treatment	101	257	358
Excellent	72 ( 71.3)	225 ( 87.5)	297 ( 83.0)
Good	21 ( 20.8)	19 ( 7.4)	40 ( 11.2)
Moderate	3 ( 3.0)	6 ( 2.3)	9 ( 2.5)
Poor/no response	0	1 ( 0.4)	1 ( 0.3)
Missing	5 ( 5.0)	6 ( 2.3)	11 ( 3.1)

Source: Original BLA 125582/0; CSL654\_3001 Study Report Body, Table 11–16, p.122

- rIX-FP consumption during routine prophylaxis

For subjects in Arm 1, the mean (SD) total monthly consumption (IU/kg) of rIX-FP was 202.7 (47.92), 201.5 (42.56), and 157.4 (16.34) for the 7-, 10-, and 14-day prophylaxis regimens, respectively. The corresponding mean for the prophylaxis regimen in Arm 2 was 191.7 (36.33) IU/kg. The monthly consumption was 320.7 (208.75) IU/kg for previous FIX based on 28 subjects. The applicant claimed that subjects on routine prophylaxis with rIX-FP had lower monthly consumption compared with previous FIX product.

- Comparison of AsBR between the 7-day and >7-day prophylaxis regimens

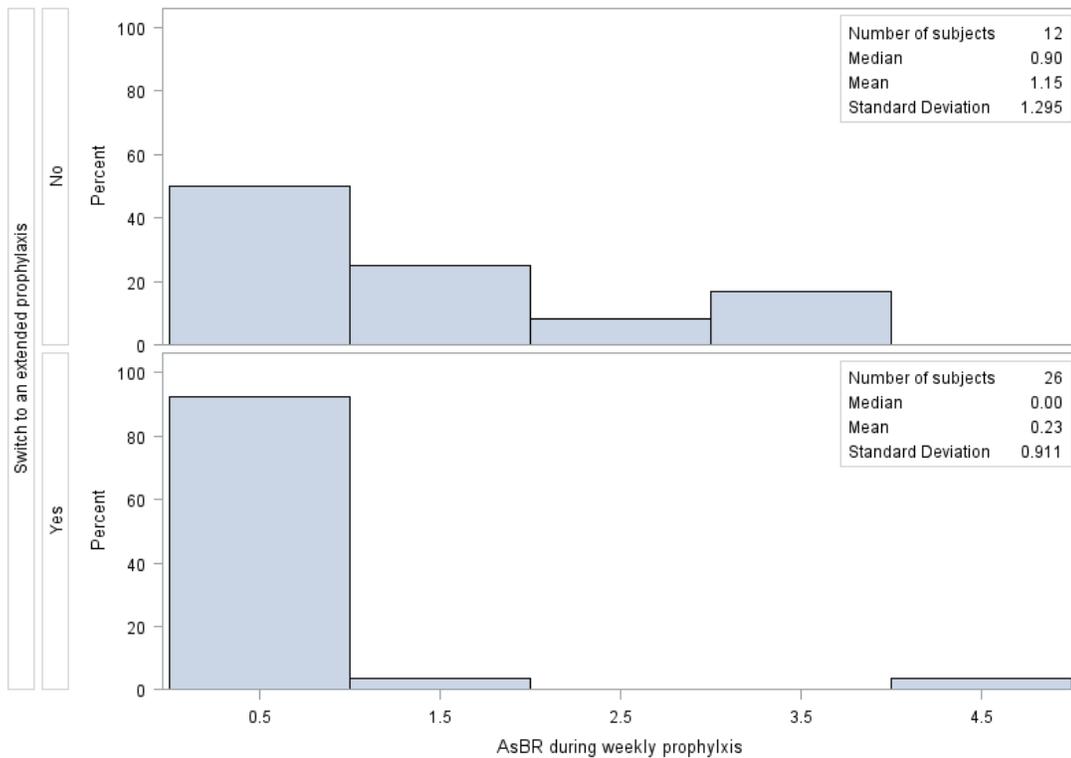
This analysis was performed on the Efficacy population in subjects in the prophylaxis treatment arm (Arm 1) with at least 12 weeks of treatment on more than 1 regimen (n=26). The mean duration was 267 days (range: 114-413; n=7) for the 10-day regimen and was 354 days (range: 98-575; n=21) for the 14-day regimen. Two subjects had both the 10-day and 14-day regimens. The result was not updated with additional data from the three subjects in Study 3003.

Non-inferiority to the weekly prophylaxis was demonstrated for the combined extended treatment (every 10 or 14 days), and the 10-day or 14-day prophylaxis treatment alone. The mean AsBR was 0.23 for the 7-day treatment regimen and 0.85 for the extended treatment regimens with a mean difference of -0.62 (95% CI, -1.411, 0.163). The mean AsBR difference of the 7-day (0.00) versus 10-day (0.13)

prophylaxis treatment regimens was -0.13 (n=7). The mean AsBR difference of the 7-day (0.28) versus 14-day (1.07) prophylaxis treatment regimens was -0.79 (n=21).

Among the 14 subjects who did not switch to any extended prophylaxis treatment regimen, 2 of them had missing data of AsBR during weekly prophylaxis. The comparison of AsBR during weekly prophylaxis between these 12 (14-2) subjects and those 26 subjects who switched is presented in the histograms in Figure 2, based on my analysis. It is noted that subjects who switched to extended prophylaxis had less frequent bleedings during weekly prophylaxis.

**Figure 2.** AsBR histograms for subjects who did not and did switch to an extended prophylaxis regimen



- ABR and AsBR in Arm 1 and Arm 2

The applicant reported the bleeding rate for both arms across all bleeding categories (total, spontaneous, traumatic, joint, and spontaneous/unknown); Table 7 presents only total bleeding and spontaneous bleeding which required treatment. The result was not updated with additional data from the three subjects in Study 3003.

**Table 7. ABR and AsBR in Arm 1 and Arm 2 (Efficacy Population)**

	Prophylaxis (Arm 1)			On-demand (Arm 2)	
	7-day regimen (N=40)	10-day regimen (N=7)	14-day regimen (N=21)	On-demand regimen (N=23)	Prophylaxis regimen (N=19)
<b>Total bleeding episodes</b>					
Annualized bleeding rate (bleeding episodes/year) per subject					
n	38	7	21	22	18
Mean (SD)	1.24 (1.780)	0.82 (1.195)	1.96 (2.653)	20.28 (8.616)	2.87 (4.954)
Median	0.00	0.00	1.08	18.65	1.19
Q1, Q3	0.00, 1.87	0.00, 1.78	0.00, 2.70	16.70, 25.53	0.00, 4.06
Min, Max	0.0, 6.0	0.0, 3.0	0.0, 9.1	2.0, 46.1	0.0, 21.1
<b>Spontaneous bleeding episodes</b>					
Annualized bleeding rate (bleeding episodes/year) per subject					
n	38	7	21	22	18
Mean (SD)	0.52 (1.116)	0.13 (0.334)	1.07 (2.114)	13.26 (8.613)	0.73 (1.205)
Median	0.00	0.00	0.00	11.57	0.00
Q1, Q3	0.00, 0.00	0.00, 0.00	0.00, 1.00	7.69, 17.03	0.00, 0.96
Min, Max	0.0, 4.5	0.0, 0.9	0.0, 7.3	0.0, 39.5	0.0, 4.2

Source: Original BLA 125582/0; CSL654\_3001 Study Report Body, Table 11–11, p.110

*Reviewer’s comment: AsBR was similar between the two arms. ABR was higher in Arm 2 compared to Arm 1 during weekly prophylaxis (mean ABR 2.87 vs. 1.24) which was not expected because subjects in Arm 2 were expected to bleed less often than subjects in Arm 1 due to the assignment criteria. This high mean ABR for Arm 2 was primarily due to an outlier: subject (b) (6) had an ABR of 21.07 during 260 days of prophylaxis treatment. With this subject excluded, the mean ABR for Arm 2 was reduced from 2.87 to 1.79.*

- Investigator’s assessment of hemostatic efficacy for surgical prophylaxis

A total of four subjects reported six surgeries during the study, two of which were related to hemophilia. Hemostatic efficacy for surgical prophylaxis was rated as excellent or good for all surgeries at wound closure, 72 hours post-surgery, and at the end of the surgery sub-study (Day 14). No other hemostatic interventions or transfusion support were required for any subject.

#### 6.1.11.3 Subpopulation Analyses

- Subgroup analysis by age, race, and region

All the subjects in the Primary Efficacy population were adults ( $\geq 18$  years). Three of them were Asian while the remaining 16 subjects were white and from either the US (3) or Europe (13). Similar efficacy was observed among subgroups by race and region.

For one secondary efficacy endpoint, number of infusions of rIX-FP to achieve hemostasis in the treatment of minor/moderate bleeding episodes, all five bleeding episodes which required  $>2$  infusions to achieve hemostasis occurred on four adult subjects.

For another secondary efficacy endpoint, the investigator reported the hemostatic efficacy as excellent or good for 86% (12/14) for the bleeding episodes treated in the pediatric population (12-18 years old) and 94% (325/344) for the adult population (>18 years old). It should be pointed out that the two bleeding episodes from pediatric subjects that were not rated as excellent or good by investigators were actually missing values but they were treated as non-effective in the calculation.

#### 6.1.11.4 Dropouts and/or Discontinuations

A total of 8/63 (12.7%) subjects discontinued the study (3/40 [7.5%] in the prophylaxis treatment group and 5/23 [21.7%] in the on-demand treatment group). The reasons for discontinuation were presented in Figure 1. Considering the extremely significant efficacy of rIX-FP observed and the reasons of dropout, the efficacy conclusion should be robust to these dropouts and there is no need to conduct any additional sensitivity analyses.

#### 6.1.12 Safety Analyses

The extent of exposure (mean [SD]) was 72.4 (22.11) and 51.5 (30.63) EDs in the prophylaxis and on-demand treatment groups, respectively. Most subjects in the prophylaxis treatment group had  $\geq 50$  EDs (37/40), and half (12/23) of the subjects in the on-demand treatment arm had  $\geq 50$  EDs.

##### 6.1.12.3 Deaths

There were no deaths.

##### 6.1.12.4 Nonfatal Serious Adverse Events

A total of two subjects had two treatment-emergent Serious Adverse Events (SAEs). Neither of these events was considered by the investigator to be related to rIX-FP.

##### 6.1.12.5 Adverse Events of Interest

No inhibitors to rIX-FP were detected among the 63 subjects in the Safety population. The predefined success criterion was met.

No subjects developed antibodies to rIX-FP or CHO host cell protein.

## 6.2 CSL654\_3002

Study 3002 was a Phase 3 study that evaluated the PK, safety, and efficacy of once weekly prophylaxis with rIX-FP in pediatric subjects (<12 years old) with Hemophilia B. Both the Safety and Efficacy populations consisted of 27 subjects who received at least 1 dose of rIX-FP during the study. Two subjects (both 6 to <12 years of age) participated in the surgical sub-study.

Subjects had a mean age of 5.9 years. Twelve subjects were <6 years of age, and 15 subjects were 6 to <12 years of age. The majority of subjects received previous FIX as routine prophylaxis treatment prior to study entry (24/27 subjects, 88.9%).

The overall median AsBR was 0.00; 51.9% of subjects did not experience a spontaneous bleeding episode during the treatment period of 8-18 months. More spontaneous bleeding episodes were experienced by subjects 6 to <12 years of age (median AsBR: 0.78) than by subjects <6 years of age (median AsBR: 0.00). The majority of bleeding episodes in the Efficacy population (103/106; 97.2%) were successfully treated with one or two injections of rIX-FP. For most bleeding episodes requiring treatment, the Investigator's assessment of hemostatic efficacy of rIX-FP was either excellent (78/104, 75.0%) or good (22/104; 21.2%).

No inhibitors against FIX or treatment-emergent antibodies against rIX-FP were reported for any subject during the study. There were no deaths and no withdrawals due to AEs. Four subjects reported six treatment-emergent serious adverse events (SAEs). None of the treatment-emergent SAEs were considered by the Investigator to be related to rIX-FP.

### **6.3 CSL654\_3003**

Study 3003 is an ongoing Phase 3b long-term extension study that is evaluating the safety and efficacy of rIX-FP for routine prophylaxis and on-demand treatment of bleeding episodes in subjects with Hemophilia B. Subjects from studies 3001 and 3002 are eligible for enrollment. In addition, subjects who have not previously completed a CSLB-sponsored rIX-FP lead-in study are eligible to enter the study if they require major non-emergency surgery, or if they are previously untreated subjects who meet the eligibility criteria. Prophylaxis subjects are enrolled into Arm 1 (from Arm 1 of Study 3001 and Study 3002), and on-demand subjects are enrolled into Arm 2 (from Arm 2 of Study 3001). Arm 3 is for the surgery substudy.

A total of 81 subjects were enrolled in Study 3003, 80 of whom were treated with at least 1 dose of rIX-FP (Safety population). Subjects had a mean age of 27.5 years (min, max: 2, 63 years). All subjects in Arm 2 (n=16) and Arm 3 (n=4) were  $\geq 12$  years of age, while Arm 1 included 24 subjects <12 years of age and 36 subjects  $\geq 12$  years of age. At the data cutoff date (January 9, 2015), 7 subjects had participated in the surgical sub-study.

Since the data lock point, there has been development of FIX inhibitor in a previously untreated subject. The subject is an 11-year-old Asian male diagnosed with Hemophilia B (FIX level < 2%) in July 2013. Prior to receiving rIX-FP, he had not received any FIX replacement product to treat his Hemophilia B. The low titer inhibitor was reported as a related SAE on August 06, 2015. This subject reported hypersensitivity as well.

*Reviewer's comment: based on the clinical reviewer's input, the previously untreated subjects have a higher risk of inhibitor development compared to previously treated subjects, while the regulatory decision is mainly based on the latter. I defer to the clinical reviewer regarding whether and how this will impact product approval and the labeling.*

There were no deaths. Two other treatment-emergent SAEs were reported for two subjects; neither was considered by the Investigator to be related to rIX-FP, and neither led to study drug withdrawal.

## 7. INTEGRATED OVERVIEW OF EFFICACY

### 7.1 Response to prophylaxis treatment

Studies 2004 and 3001 both provided data comparing AsBR between groups of subjects taking rIX-FP on an on-demand basis with those taking it in a prophylaxis regimen. In Study 2004, the comparison was between independent groups, while in Study 3001, the comparison was within subjects. The mean AsBR in Study 2004 for the weekly prophylaxis was higher than that in Study 3001, as shown in Table 8 below.

*Reviewer's comment: it should be pointed out that the weekly prophylaxis dose in Study 2004 was 15 to 35 IU/kg, adjusted up to a maximum of 75 IU/kg, which was lower than that in Study 3001 (35-50 IU/kg, adjusted up to a maximum of 75 IU/kg).*

**Table 8.** Response to prophylaxis treatment

	Study number			
	2004		3001	
	On-demand (N=4)	Weekly Prophylaxis (N=13)	On-demand (N=23)	Weekly Prophylaxis (N=59)
<b>Total number of subjects with spontaneous bleeding episodes requiring treatment (N[%])</b>	4 (100)	7 (53.8)	22 (95.7)	17 (28.8)
<b>Annualized spontaneous bleeding rate (bleeding episodes/year/subject)</b>				
N	4	13	22	56
Mean	21.740	1.255	13.26	0.59
SD	3.9983	1.4967	8.613	1.139
Median	22.218	1.134	11.57	0
Q1, Q3	18.737, 24.743	0.000, 2.269	7.69, 17.03	0, 0.75
Min, Max	16.60, 25.92	0, 4.52	0, 39.5	0, 4.5

Source: Original BLA 125582/0; 2.7.3 Summary of Clinical Efficacy, adapted from Table 3–5, p.34

### 7.2 Control of bleeding episodes

Bleeding episodes in both Study 2004 and Study 3001 were treated with rIX-FP as they occurred. All bleeding episodes in both studies were classified as “minor” or “moderate”. All the bleeding episodes in Study 2004 required either 1 or 2 injections to achieve hemostasis. The proportion of bleeding episodes whose treatment was classified as “excellent” by the investigators was only 62.4% (53/85) in Study 2004, but was 83.0% (297/385) in Study 3001 (Table 9). However, 34.1% (29/85) and 11.2% (40/358) of bleeding episode treatment was assessed by the investigators as “good” in Studies 2004 and 3001, respectively.

Reviewer's comment: it should be pointed out that the on-demand treatment dose in Study 2004 was  $\geq 25$  IU/kg which was probably lower than that in Study 3001(35-50 IU/kg).

**Table 9.** Control of Bleeding Episodes with rIX-FP

		Study Number		
		2004 (N=17 subjects)	3001 (N=63 subjects)	2004 & 3001 (N=65* subjects)
Number of bleeding episodes		85	358	443
Bleeding episodes requiring treatment	1 injection (%)	76 (89.4)	335 (93.6)	412 (93.0)
	2 injections (%)	9 (10.6)	18 (5.0)	26 (5.9)
	>2 injections (%)	0	5 (1.4)	5 (1.1)
Assessment of hemostatic efficacy	Excellent (%)	53 (62.4)	297 (83.0)	350 (79.0)
	Good (%)	29 (34.1)	40 (11.2)	69 (15.6)
	Moderate	3 (3.5)	9 (2.5)	12 (2.7)
	Poor	0	1 (0.3)	1 (0.2)
	Missing	0	11 (3.1)	11 (2.5)

\*: majority of the subjects from 2004 participated in 3001.

Source: Original BLA 125582/0; 2.7.3 Summary of Clinical Efficacy, adapted from Table 3–9, p.40

### 7.3 Perioperative management of bleeding

There were 15 surgeries in the rIX-FP clinical development program, including 12 surgeries in adults (Studies 3001 and 3003) and 3 surgeries in children <12 years (Study 3002). Prior to the surgical procedure, the subject received a single bolus injection of rIX-FP in the range of 50 to 75 IU/kg in order to increase FIX activity to 60% to 80%. Additional bolus injections of rIX-FP could be given during surgery, if needed. Hemostasis was assessed by the investigator/surgeon at wound closure, 72 hours after surgery, or at hospital discharge and at the end of the surgical sub-study using a 4-point scale of excellent, good, fair, and none. Hemostatic efficacy was rated excellent or good for all surgeries at all available time points.

## 10. CONCLUSIONS

### 10.1 Statistical Issues and Collective Evidence

All of the following comments apply to pivotal Study 3001.

1. I verified the analyses of primary and secondary efficacy endpoints, based on the data sets included in the original submission.
2. The study met the acceptance criteria for the primary efficacy endpoint (AsBR) and primary safety endpoint (inhibitor rate). Prophylaxis treatment significantly reduced the AsBR compared to the on-demand treatment regimen based on paired analysis. The result was robust to sensitivity analyses.
3. In the Efficacy population, most of the bleeding episodes (353/358, 98.6%) were treated successfully with 1 or 2 infusions of rIX-FP. The investigators reported

that the rIX-FP treatment was effective (excellent or good) for 94.1% (337/358) of the bleeding episodes.

4. For the primary efficacy endpoint (AsBR) and the above two hemostatic endpoints, all subgroups by race and region had similar efficacy.
5. The applicant compared the AsBR of different prophylaxis regimens among 26 subjects in the prophylaxis arm (Arm 1) who switched from weekly prophylaxis to an extended treatment interval (10-day or 14-day). Compared to the other 12 subjects in Arm 1 who did not switch to any extended prophylaxis treatment regimen, these 26 subjects bled less frequently during weekly prophylaxis (see Figure 2). If those 12 subjects had switched as well, the efficacy would not be as good as observed. As discussed with the clinical reviewer, if the extended prophylaxis interval indication is approved, the labeling should reflect the fact that the results were based on a subgroup of subjects who met pre-specified switching criteria, and may not be generalizable to the Hemophilia B population at large. In addition, it may be necessary to separate the reporting for 10-day and 14-day treatment regimens in the labeling.
6. The ABR was higher in the on-demand arm (Arm 2) compared to the prophylaxis arm (Arm 1) during weekly prophylaxis (mean ABR 2.87 vs. 1.24, respectively). This was primarily due to one outlier from Arm 2: subject (b) (6) with an ABR of 21.07 during 260 days of prophylaxis treatment. With this subject excluded, the mean ABR from Arm 2 was reduced from 2.87 to 1.79. This subject experienced 15 (12 traumatic and 3 spontaneous) and 14 (2 traumatic and 12 spontaneous) bleeding episodes during the 260 days of weekly prophylaxis treatment and 111 days of on-demand treatment, respectively. Most of them were joint bleeds requiring treatment.
7. The applicant claimed that subjects had less consumption of FIX products during routine prophylaxis in this study compared to prior treatment. This claim cannot be made for the three reasons: 1) it is not based on paired analysis; 2) it is not pre-specified; and 3) it is not based on formal hypothesis testing. It is noted that this claim is not included in the proposed label.

The following comment applies to Study 3002, the pediatric study:

8. Among the 27 subjects who received at least 1 dose of rIX-FP, the median AsBR was 0.00; 51.9% of subjects did not experience a spontaneous bleeding episode during the treatment period of 8-18 months. 97.2% (103/106) of bleeding episodes were successfully treated with one or two injections of rIX-FP. For most bleeding episodes requiring treatment, the investigator's assessment of hemostatic efficacy of rIX-FP was either excellent (78/104, 75.0%) or good (22/104; 21.2%).

The following comments apply to all the studies:

9. Hemostatic efficacy was rated either excellent or good by investigators for all the 15 surgeries at all available time points.
10. No inhibitors against FIX or treatment-emergent antibodies against rIX-FP were reported in the 111 previously treated subjects in the five studies covered in this

review. One previously untreated subject from the ongoing study (3003) reported a low titer inhibitor against factor IX.

## **10.2 Conclusions and Recommendations**

No major statistical issues were identified during the review of this BLA. No clarifications are required from the applicant. The statistical results from this BLA appear to support the claim for use of rIX-FP in the treatment of Hemophilia B patients for routine prophylaxis to prevent or reduce the frequency of bleeding episodes, on-demand treatment and control of bleeding episodes, and perioperative management of bleeding. If the extended prophylaxis interval indication (10-day and/or 14-day) is approved, we recommend that the labeling reflect the fact that the results were based on a subgroup of subjects who met pre-specified switching criteria, and may not be generalizable to the Hemophilia B population at large.