Statistical Review, August 2013 - Alprolix

Application Type	BLA
STN	125444
CBER Received Date	Dec 28, 2012
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Division / Office	DB/OBE
Priority Review	N/A
Reviewer Name(s)	Judy X. Li, PhD
Review Completion Date / Stamped Date	Aug 20, 2013
Supervisory Concurrence	Renee Rees, PhD Boguang Zhen, PhD Estelle Russek-Cohen, PhD
Applicant	Biogen Idec, Inc.
Established Name	rFIXFc
(Proposed) Trade Name	ALPROLIX

Dosage Form(s) and Route(s) of Administration	ALPROLIX is supplied as a lyophilized powder in single use vials containing nominally 500, 1000, 2000, and 3000 IU
Indication(s) and Intended Population(s)	Treatment of hemophilia B

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Glossary

1. Executive Summary

The primary efficacy endpoint was a comparison of annualized bleeding rates between each of two prophylaxis arms and the on demand treatment arm. There was a statistically significant reduction in the estimated annualized bleeding rate for subjects in both prophylactic arms with an 83% reduction in annualized bleeding rate for the weekly prophylaxis regimen (Arm 1) and an 87% reduction for the individualized interval prophylaxis regimen (Arm 2) compared with on demand treatment (Arm 3). The safety evaluation revealed that no subject developed an inhibitor. There is no statistical concern in the review of this submission.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia B (Christmas Disease) is a congenital bleeding disorder occurring predominantly in males, characterized by a deficiency of Factor IX (FIX). Hemophilia results in abnormal clot formation, causing prolonged and abnormal bleeding including bleeding into joints, soft tissue, muscle, and body cavities. Bleeding episodes may be associated with trauma or occur in the absence of trauma (spontaneous bleeding). Bleeding may be life-threatening or result in significant morbidity, such as neurologic deficits (following a central nervous system [CNS] bleeding episode) or arthropathy (resulting from recurrent hemarthrosis).

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

There is no available cure for hemophilia B; treatment focuses on the replacement of FIX with FIX-containing coagulation products to promote clotting. Initially, therapy was limited to treatment of acute bleeding episodes (episodic, or on-demand, treatment) through intravenous (IV) administration of a FIX-containing product. The current recommended standard of care involves the regular administration of recombinant FIX (prophylaxis) to minimize the number of bleeding episodes. Prophylaxis has been associated with improvements in long-term outcomes, but is hindered by the need for frequent IV administration of factor. The development of FIX-neutralizing antibodies (inhibitors), seen in a minority of patients in response to therapy, creates significant

challenges for both on demand and prophylactic therapies, due to lack of response to therapy with FIX concentrates.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The original protocol of the Phase 3 clinical efficacy study (Protocol 998HB102, Version 1.0) was submitted on 5 November 2012 under IND # 13487, and there were six amendments subsequently. A Type B pre-BLA meeting on 14 June 2012 included a discussion on a revised statistical analysis plan with an additional interim analysis for the assessment of inhibitor risk in the phase 3 study. FDA accepted Biogen's overall two-stage analysis plan and the proposed analysis methodology for the primary efficacy objectives in the phase 3 study. FDA also stated that at the time of the BLA submission, data from at least 50 subjects with 50 exposure days should be submitted and data from 20 additional subjects with 50 exposure days must be submitted not less than three months before the action due date. In addition, FDA stated that Biogen may not be able to make a claim of "superiority as statistically relevant", but Biogen may instead state that there is a 50% reduction in the annualized bleeding rate. On 07 August 2012, Biogen submitted a revised statistical analysis plan to IND #13487. A number of further exploratory endpoints not originally specified in the protocol for the analysis of annualized bleeding rates were included. A formal statistical analysis of the number of annualized bleeding episodes based strictly on all bleeds as recorded was also added. On 01 July 2013, FDA sent an Information Request letter asking Biogen to clarify the number of subjects within each study arm who completed the study 99HB102. An amendment with this information was received on 9 August 2013.
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3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission is adequately organized for conducting a complete statistical review of the primary efficacy endpoint without reasonable difficulty.
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5. Sources of Clinical Data and Other Information Considered in the Review

All data sources are included in the sponsor's eCTD submission located in the FDA/CBER Electronic Document Room (EDR).

5.1 Review Strategy

There are four clinical studies in the submission: completed phase 1/2a study SYN-FIXFc-0007-01; completed phase 3 study 998HB102; ongoing pediatric study 9HB02PED and ongoing study 9HB01EXT which is an extension to study 998HB102. For details of each study refer to Section 5.3. Data pertaining to the PK, safety, and efficacy of rFIXFc are drawn from the two completed clinical studies. However, the phase 1/2a study did not materially impact the analysis or the conclusions of the review. Therefore it is not included in this review memo. For the ongoing pediatric study, a progress report including summary statistics was submitted. No formal statistical analysis was conducted. Per discussion with the primary clinical reviewer, this review memo only focuses on the analysis of the primary endpoints of the completed pivotal phase 3 study 998HB102.

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

The study report 998HB102 (module 5.3.5.2) was reviewed and data files adef.xpt, adsl.xpt, adhh.xpt (module 5.3.5.2) were used for the verification of the analysis results for the primary efficacy endpoint.

5.3 Tables of Studies/Clinical Trials

The following studies are included in the submission:
Completed Studies:
(1) Study SYN-FIXFc-0007-01 was a phase 1/2a, open-label, multicenter, safety, dose-escalation study that evaluated the safety and PK of a single dose of rFIXFc in 14 previously treated patients (PTPs) with severe hemophilia B (defined as ≤2 IU/dL [≤2%] endogenous FIX). The subjects were 18 years of age or older, with at least 100 prior exposure days (EDs) to a FIX product.
(2) Study 998HB102 was a phase 3, open-label, global, multicenter study that evaluated the safety, PK, and efficacy of rFIXFc in 123 PTPs with severe hemophilia B (defined as ≤2% endogenous FIX), ≥12 years of age, with at least 100 prior EDs to a FIX product. The study compared the annualized bleeding rate between subjects receiving a weekly prophylaxis regimen or an individualized interval prophylaxis regimen versus subjects on an episodic (on-demand) regimen. Hemostatic response to rFIXFc during surgery and throughout the perioperative period was also evaluated.
Ongoing Studies:
(3) Study 9HB02PED is an open-label, multicenter study evaluating the safety, PK, and efficacy of rFIXFc in pediatric PTPs who are younger than 12 years of age with severe hemophilia B (defined as ≤2% endogenous FIX) and have had at least 50 EDs to FIX products prior to enrollment. At least 20 subjects are planned: 10 subjects <6 years and 10 subjects 6 years to <12 years of age.
(4) Study 9HB01EXT is an open-label, multicenter extension to the phase 3 study (998HB102) and the pediatric study (9HB02PED) evaluating the long-term safety of rFIXFc for prophylaxis and on demand treatment of bleeding episodes in PTPs with hemophilia B.

This review memo only focuses on the analysis of the primary endpoints of the completed pivotal phase 3 study 998HB102.

6. Discussion of Individual Studies/Clinical Trials

6.1 Study 998HB102

6.1.1 Objectives (Primary, Secondary, etc)

The primary objectives of the study are to evaluate the safety and tolerability of rFIXFc; to evaluate the efficacy of rFIXFc in all treatment arms; and to evaluate the effectiveness of prophylaxis over on-demand therapy by comparing the annualized number of bleeding episodes between subjects receiving rFIXFc on each prophylaxis regimen (Arm 1 and Arm 2) and subjects receiving rFIXFc on an on-demand regimen (Arm 3).
The secondary objectives of the study are to evaluate and assess the PK parameter estimates of rFIXFc and BeneFIX at baseline in the Sequential PK subgroup as well as rFIXFc at Week 26 (± 1 week); to evaluate subjects' response to treatment; and to evaluate rFIXFc consumption.

6.1.2 Design Overview

The study is an open-label, multi-center study that evaluates the safety, tolerability, pharmacokinetics, and efficacy of rFIXFc in subjects with severe Hemophilia B.
All subjects were to receive study treatment according to the assigned treatment group:
Arm 1, Weekly Prophylaxis
- 50 IU/kg rFIXFc once every 7 days initially, then at a dose indicated by the subject's baseline PK assessment that ensured a target trough of 1% to 3% above baseline or higher
- Sequential PK subgroup, at selected sites, for PK profiling:
Single dose of 50 IU/kg BeneFIX at baseline prior to first dose of rFIXFc Single dose of 50 IU/kg rFIXFc, a minimum of 120 hours following BeneFIX dose Single dose of 50 IU/kg rFIXFc at Week 26
Arm 2, Individualized Interval Prophylaxis
- 100 IU/kg rFIXFc once every 10 days initially, then at an interval derived from the baseline PK assessment that ensured a target trough of 1% to 3% above baseline or higher
Arm 3, On Demand Regimen
- 20 to 100 IU/kg rFIXFc, or the dose indicated by the subjects' baseline PK to target a plasma level of 20% to 100%, as needed for the treatment of mild to severe bleeding episodes
Arm 4, Perioperative Management
- 40 to 100 IU/kg rFIXFc, as needed for the surgical prophylaxis (perioperative management) and treatment of bleeding episodes

The overall study duration was to be approximately 72 weeks, including the screening, treatment, and follow-up periods. The duration of the treatment period was dependent upon the treatment arm, in addition to meeting the end of study definition

Statistical Reviewer Comment: *The study is not a randomized control study. Subjects were to be assigned to treatment arms according to the standard of care and investigator decision. Study results from such a design could contain potential bias or confounding issues due to the lack of randomization.*

6.1.3 Population

Candidates were required to have met the following criteria at screening to be eligible for the study:
1. Able to understand the purpose and risks of the study and to provide signed and dated informed consent and authorization to use protected health information in accordance with national and local subject privacy regulations. If the subject was younger than 18 years of age, then a parent or guardian was to have signed the ICF and the subject was to have signed the assent form as consistent with local authorities.
2. Male, 12 years of age or older, and weighing at least 40 kg
3. Severe hemophilia B, defined as ≤2 IU/dL (≤2%) endogenous FIX activity, as determined from the central laboratory at the time of screening. If the screening result was >2%, then the severity of hemophilia B was to have been confirmed by documented historical evidence from a certified clinical laboratory demonstrating ≤2% factor IX coagulant activity, by the medical record, or by a documented genotype known to produce severe hemophilia B.
4. A PTP, defined as having at least 100 prior exposure days (EDs) to any recombinant or plasma-derived FIX product (fresh frozen plasma treatment was not to be considered in the count of the documented EDs)
5. Bleeding events and/or treatment with FIX during the prior 12 weeks, as documented in the subject's medical records
6. Greater than or equal to eight bleeding episodes in the 52 weeks prior to enrollment in the study, if treating with an on-demand (episodic) regimen
7. A platelet count ≥100,000 cells/μL
8. Immunocompetent, as determined by the Investigator's review of the subject's medical history
9. Viral load of <400 copies/mL, if HIV antibody positive
10. An international normalized ratio <1.40, as defined by the testing laboratory's normal range
11. Subjects entering directly into Arm 4 (Surgery) were to have met all other eligibility criteria AND required major elective surgery.

6.1.6 Sites and Centers

A total of 123 male subjects were enrolled at 50 investigational sites in 17 countries worldwide. The highest enrolling countries were the United States (35 subjects), Great

Britain (13 subjects), South Africa (9 subjects), Brazil (8 subjects), China (7 subjects), Hong Kong (7 subjects), and India (7 subjects).

6.1.8 Endpoints

Primary Endpoints
The primary efficacy endpoint is:
- Number of bleeding episodes (spontaneous and traumatic) with rFIXFc per subject annualized over the study period (comparison of Arm 1 vs. 3 and Arm 2 vs. 3)
Safety and tolerability endpoints include:
- Clinically notable changes from baseline in laboratory values
- Incidence of Adverse events (AEs)
- Incidence of inhibitor development

Secondary Endpoint(s)
- Assessments of response to treatment with rFIXFc for bleeding episodes, using the 4-point bleeding response scale (Excellent: Abrupt pain relief and/or improvement in signs of bleeding within approximately 8 hours after the initial injection; Good: Definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after an injection, but possibly requiring more than one injection after 24 to 48 hours for complete resolution; Moderate: Probable or slight beneficial effect within 8 hours after the initial injection and requiring more than one injection; No response: No improvement, or condition worsened, within approximately 8 hours after the initial injection)
- Physicians' global assessments of subjects' response to treatment with rFIXFc, using a 4-point scale (Excellent: bleeding episodes responded to less than or equal to the usual number of injections or less than or equal to the usual dose of rFIXFc, or the rate of breakthrough bleeding during prophylaxis was less than or equal to that usually observed; Effective: most bleeding episodes responded to the same number of injections and dose, but some required more injections or higher doses, or there was a minor increase in the rate of breakthrough bleeding; Partially Effective: bleeding episodes most often required more injections and/or higher doses than expected, or adequate breakthrough bleeding prevention during prophylaxis required more frequent injections and/or higher doses; Ineffective: routine failure to control hemostasis or hemostatic control required additional agents)
- Total annualized rFIXFc consumption per subject
- Dose per injection for Arm 1
- Dosing interval for subjects in Arm 2
- The number of annualized spontaneous bleeding episodes (joint, soft tissue, and muscle) per subject
- The number of annualized joint bleeding episodes (spontaneous and traumatic) per subject
- Time from last injection of rFIXFc to the bleeding episode
- Number of injections and dose per injection of rFIXFc required to stop a bleeding episode (joint, soft tissue, and muscle)
- Quality-of-Life (QoL) via Hemophilia-Specific QoL index questionnaires for children (Haemo-QoL) or adults (Haem-A-QoL) for Arms 1 and 2

6.1.9 Statistical Considerations & Statistical Analysis Plan

The following analysis was conducted by Biogen per the statistical analysis plan pre-specified in the latest version of the protocol:

Primary Efficacy Endpoint Analysis:

The number of bleeding episodes was annualized for each subject using the following formula:

Annualized bleeding rate = x365.25

Number of bleeding episodes during the efficacy period

Total number of days during the efficacy period

The comparison of annualized bleeding rates between the 2 prophylaxis regimens (Arms 1 and 2) and the on-demand regimen (Arm 3) were performed in a hierarchical, step-down fashion as follows:

The analysis proceeded by comparing annualized bleeding rates between Arm 1 (Weekly Prophylaxis) and Arm 3 (On Demand Regimen) using a Poisson regression model with treatment arm as a covariate. If the treatment factor in the Poisson regression model failed to show statistical significance at the 2-sided 5% level based on a contrast between Arms 1 and 3, then testing was to stop and the study would have failed to demonstrate a difference between any prophylaxis regimen and the on demand regimen. If statistical significance was shown and the estimated ratio of annualized bleeding episodes was less than 0.5 for Arm 1: Arm 3, then clinical importance of the weekly prophylaxis regimen would have been demonstrated. If the treatment factor in the model was significant at the 2-sided 5% level, then testing was to proceed to the comparison of Arm 2 (Individualized Interval Prophylaxis) with Arm 3 (On Demand Regimen) in the same fashion. If the treatment contrast in the model for Arm 2 versus Arm 3 was significant at the 2-sided 5% level and the estimated ratio of the annualized bleeding rates was less than 0.5 for Arm 2: Arm 3, then clinical importance of the individualized interval prophylaxis regimen would have been demonstrated. A test for over-dispersion was to be conducted to check the fit of the model. If no over-dispersion was detected at the 2-sided 5% level of significance, results from the Poisson regression model were to be used. Otherwise, a negative binomial model, which accounts for over-dispersion was to be used. Test results were tabulated by treatment arm along with the annualized bleeding rate ratios and the 95% CIs.

Statistical Reviewer Comment: *Previously FDA agreed with Biogen that the comparison of the annualized bleeding rates between the two prevention regimens (Arms 1 and 2) and the on demand regimen (Arm 3) be conducted in a hierarchical and step-down fashion. When more than one treatment is compared to the control at the same time, a multiple comparison adjustment should be performed in order to control the overall family-wise type I error. However, since the comparison pre-specified in the statistical analysis plan was to be conducted in a hierarchical and step-down approach, an analysis without multiple adjustments is acceptable.*

Exploratory Sensitivity Analyses of the Primary Efficacy Endpoint

Sensitivity analyses were performed for the annualized bleeding rate:

- based on all bleeds as recorded by the subject
- excluding subjects with major protocol deviations potentially impacting the primary efficacy endpoint

- for the last 6 months on study for subjects with at least 9 months on study, and for the last 3 months on study for subjects with at least 6 months on study
- by the prophylactic dose compliance rate (<80%, ≥80%, Arms 1 and 2), by the prophylactic dosing interval compliance rate (<80%, ≥80%, Arms 1 and 2), and by the overall prophylactic dose and dosing interval compliance rate (<80%, ≥80%, Arms 1 and 2)

Exploratory Subgroup Analyses of the Primary Efficacy Endpoint Subgroup analyses were performed for the annualized bleeding rate:

- by most recent prestudy treatment regimen
- by severity of hemophilia at baseline (estimated bleeds in the prior 12 months; 0, 1 to 11, 12 to 23, 24 to 35, ≥36)
- by the number of target joints (none present, ≤median of the number present, >median of the number present)
- by age (12-17 years, 18-64 years, 65 years and older)

Primary Safety Endpoint Analysis:

A group sequential approach was applied to assess inhibitor risk. The hypotheses to be tested at a one-sided 0.025 level were:

H0: Inhibitor incidence ≥ 10.65%

Ha: Inhibitor incidence < 10.65%

The stopping criteria at the first interim analysis (N1 =34) was pre-specified to allow no subjects with a confirmed inhibitor in the first N1 subjects to reach 50 EDs. The stopping criteria for the second interim analysis (N2 =50) was pre-specified to allow up to one subject with an inhibitor in the combined subjects (N1+N2 = 84) to reach 50 EDs. The stopping criteria at the final analysis (N3) was pre-specified to allow up to two subjects with an inhibitor in the combined total subjects (N1 + N2 + N3) to reach 50 EDs. If any of these stopping criteria were met, the null hypothesis would be rejected in favor of the alternative and, providing that all other criteria were satisfied in the End of Study definition, the study would be stopped. If the study was deemed to be able to stop after the first interim analysis, a final End of Study analysis was to be performed, which would correspond to the time of second interim analysis. This would ensure that the minimum requirement for provision of data to assess inhibitor risk was provided.

Due to the sequential nature of this design the maximum likelihood estimator for the true inhibitor incidence is generally biased and the usual confidence intervals calculated without adjusting for the design do not generally achieve the nominal confidence level. Therefore, the point estimate and exact, 2-sided 95% CIs reported at the termination of this study were derived using the methods described by Jung and Kim ("On the estimation of the binomial probability in multistage clinical trials". Statistics in Medicine, 2004, 23:881-896).

Except for the estimation of inhibitor risk, no statistical hypothesis testing was performed for the safety evaluation. The 2-sided 95% CI on the inhibitor incidence rate was evaluated using the Clopper-Pearson exact method for a binomial proportion and descriptive statistics were provided for the other safety endpoints.

Determination of Sample Size:

Because of the limited number of subjects in the hemophilia B population (an estimated incidence of 1 in 25,000 male births), the sample size of this study was mainly based on clinical rather than statistical considerations. Taking into account the CPMP Note for

Guidance [CPMP/BPWG/1625/99 2000], efforts were made to collect sufficient data for assessments of the efficacy and safety of rFIXFc.

A key safety objective for any study of a new FIX product is the evaluation of inhibitor development. FDA guidance for adequate demonstration of acceptable inhibitor risk in clinical trials of previously treated FIX patients allows 1 out of 50 subjects to experience an inhibitor, with each subject requiring a minimum of 50 EDs to the study treatment. Under the assumption that the occurrence of inhibitors in a clinical study can be adequately modeled using the binomial distribution, a minimum of 50 EDs would allow for a 2-sided, 95% CI for the true inhibitor incidence of (0.05% to 10.65%) using the exact, Clopper-Pearson method if one case of inhibitor formation was observed.

Another consideration in the study sample size was the evaluation of the effectiveness of prophylaxis over on demand therapy. Using a Poisson regression model with no overdispersion, the study sample size was projected to have greater than 95% power at the 2-sided 0.05 level of significance. This was considered based on the following:

- The power was calculated for hypothesis tests between Arm 1 and Arm 3.
- It was assumed that the minimum follow-up time for subjects in Arm 1 would be 48 weeks starting from the first prophylaxis dose (10 days after the first rFIXFc dose on study), and the minimum follow-up time for subjects in Arm 3 would be 26 weeks starting from Day 1.
- An 80% retention rate was assumed; therefore, the total follow-up time of each treatment arm was calculated as 1920 subject-weeks (40 subjects) for Arm 1 and 416 subject-weeks (16 subjects) for Arm 3.
- The annualized bleeding rate for subjects in this population using on demand treatment was at least eight bleeding episodes per subject per year.

To be considered of clinical importance, there had to be at least a 50% reduction in annualized bleeding episodes.

The study enrolled 123 subjects in Arms 1-4 and a total of 115 subjects completed the study.

Randomization

Subjects were to be assigned to treatment arms according to the standard of care and Investigator decision, following discussion with each subject. Subjects receiving a prophylaxis treatment regimen prior to study start were to join Arms 1 or 2 (prophylaxis regimens) only. Subjects receiving on demand treatment prior to study start were to be allowed to enroll in Arm 1, 2, or 3 (on demand regimen). Subjects could enroll either from any of the other treatment arms into Arm 4 or as new subjects scheduled for major surgery that required FIX treatment.

Statistical Reviewer Comment: *The assignment of the treatment is not randomized and subjects receiving a prophylaxis treatment regimen prior to study start were only assigned to the prophylaxis regimens (either Arm 1 or 2). Therefore the study treatment prophylaxis effect could be potentially confounded with the pre-study treatment regimen effect. And because of the limitation of the study design, the subgroup analysis based on pre-study treatment regimen was only conducted on subjects with on demand pre-study treatment.*

Missing Data:

No imputation due to missing data was applied for analyses of efficacy endpoints.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The All-Enrolled Analysis Set was defined as subjects who were registered as enrolled and assigned a unique subject identification number. The Full Analysis Set (FAS) was defined as subjects who received at least one dose of rFIXFc. The analysis of efficacy was performed on this population. Subjects who received a dose of BeneFIX, but did not receive any rFIXFc were not included in this population.

The Safety Analysis Set was defined as subjects who received at least one dose of BeneFIX or at least one dose of rFIXFc. The analysis of safety was performed in this population.

The study enrolled 123 male subjects in Arms 1-4 and a total of 115 subjects completed the study.

6.1.10.1.1 Demographics

All subjects were male. The median age was 30 years (range 12 to 71 years), with 11 subjects (8.9%) 12 to 17 years old, 110 subjects (89.4%) 18 to 64 years old, and 2 subjects (1.6%) at least 65 years old. Of the subjects in the 12 to 17 year subgroup, 2 subjects were 12 years old, 2 were 14 years old, 3 were 15 years old, 1 was 16 years old, and 3 were 17 years old. Of the 123 subjects enrolled, 73 (59.3%) were white, 29 (23.6%) were Asian, 10 (8.1%) were black, 10 (8.1%) were classified as other, and 1 (0.8%) was American Indian or Alaska Native. The median weight was 73.30 kg (range 45.0 to 186.7 kg) and median body mass index was 24.78 kg/m2 (range 15.2 to 49.6 kg/m2). In general, the distribution of subjects was well balanced across the three main geographic regions of Europe (29.3%), North America (30.9%) and other countries (39.8%). When each region was examined by treatment arm, there were a smaller percentage of subjects in Arm 3 from Europe (7.4%) as compared with Arm 1 (33.3%) and Arm 2 (41.4%)

6.1.10.1.3 Subject Disposition

A total of 115 subjects (93.5%) completed the study and 8 subjects (6.5%) discontinued the study prematurely and distributed among study arms. The reasons for premature discontinuation were consent withdrawn (3 subjects, 2.4%), AEs (2 subjects, 1.6%), protocol violation (2 subjects, 1.6%), and lost to follow-up (1 subject, 0.8%).

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Efficacy endpoints were analyzed for 114 subjects (61 in Arm 1, 26 in Arm 2, and 27 in Arm 3). Of the 123 subjects in the Full Analysis Set, the following nine subjects did not contribute data for the efficacy period: two subjects in Arm 1, three subjects in Arm 2, and four subjects in Arm 4. The reasons for exclusion were as follows: two subjects received only 5000 rFIXFc, two subjects withdrew after their PK evaluations, one subject had a single prophylaxis dose following his PK evaluation and withdrew from the study (no efficacy assessments could be made from a single dose), and four of the six

subjects who entered directly into Arm 4 did not transition to Arm 1, 2, or 3 following their surgical/rehabilitation period.

The annualized bleeding rate was analyzed using negative binomial regression, following Wetherill and Brown's test (Wetherill, G.B. and Brown, D.W. *Statistical Process Control*, 1991; New York, Chapman and Hall, pp. 216–218) for over-dispersion in the Poisson model which indicated greater variability than would be expected from a Poisson distribution. The annualized bleeding rate estimated from the negative binomial model was 3.12 (95% CI: 2.46, 3.95) in Arm 1, 2.40 (95% CI: 1.67, 3.47) in Arm 2, and 18.67 (95% CI: 14.01, 24.89) in Arm 3. The bleeding rate ratios obtained from the model were 0.17 (p<0.001) for Arm 1 versus Arm 3, and 0.13 (p<0.001) for Arm 2 versus Arm 3, indicating that the annualized bleeding rate was significantly reduced by 83% (Arm 1) and 87% (Arm 2) using prophylaxis therapy as compared with on demand treatment. All sensitivity analyses results were consistent with the primary analysis of annualized bleeding rate.

Statistical Reviewer Comment: *The comparison of the annualized bleeding rates between the two prevention regimens (Arms 1 and 2) and the on-demand regimen (Arm 3) was conducted in a hierarchical and step-down fashion. This reviewer conducted sensitivity analyses which included the Holm-Bonferroni adjustment and Dunnett-Hsu's multiple comparison method (Hsu, J. C., Multiple Comparisons: Theory and Methods, 1996, London: Chapman & Hall) for comparing the two prevention regimens to the on demand regimen. Both procedures show that the two prevention regimens (Arm 1 and 2) are statistically significant different from the on demand regimen (Arm 3).*

6.1.11.3 Subpopulation Analyses

Subgroup analyses of the primary endpoint provide consistent results with the primary analysis of the annualized bleeding rate.

The analysis comparing annualized bleeding rates for subjects whose most recent prestudy regimen was on-demand was based on a negative binomial model. Of the subjects who participated in the efficacy period, 47% of Arm 1 and 50% of Arm 2 received on demand treatment prior to study start. The estimated annualized bleeding rate was 3.25 (95% CI, 2.38, 4.42) in Arm 1, 2.01 (95% CI, 1.22, 3.32) in Arm 2, and 18.66 (95% CI, 14.58, 23.88) in Arm 3. The bleeding rate ratios obtained from the model were 0.17 (p<0.001) for Arm 1 versus Arm 3, and 0.11 (p<0.001) for Arm 2 versus Arm 3, demonstrating an 83% (Arm 1) and 89% (Arm 2) reduction in bleeding for subjects on a prophylaxis regimen who received on demand treatment prior to study start.

Eleven subjects aged 12 to 17 years (10% of Arm 1, 12% of Arm 2, and 7% of Arm 3) and 101 subjects aged 18 to 64 years (87% of Arm 1, 88% of Arm 2, and 93% of Arm 3) participated in the efficacy period of the study. For subjects aged 12 to 17 years, the median rates of annualized bleeding rates were 2.57, 3.12, and 27.15 (the mean rates were 2.07, 4.43, and 27.15) in Arms 1, 2, and 3, respectively. For subjects aged 18 to 64 years, the median rates were 2.96, 0.72, and 16.27 (the mean rates were 3.27, 2.19, and 18.02) in Arms 1, 2, and 3, respectively.

Statistical Reviewer Comment: *This reviewer conducted additional sensitivity analyses which included the Holm-Bonferroni adjustment and Dunnett-Hsu's multiple comparison method for comparing the two prevention regimens to the on demand regimen for each age group separately (group aged 12 to 17 and group aged 18 to 64).*

For both age groups, both procedures show that the two prevention regimens (Arm 1 and 2) are statistically significant different from the on demand regimen (Arm 3). The comparison results were consistent for the two age groups.

6.1.11.4 Dropouts and/or Discontinuations

No imputation due to missing data was applied for analyses of efficacy endpoints. Four of the eight subjects who withdrew from the study did so without participation in the efficacy period of the study: two subjects from Arm 1, one subject from Arm 2, and one subject from Arm 4. Of the remaining four subjects, two participated in the efficacy period for less than 6 months; a follow-up period of at least 6 months is preferred for estimating an annualized bleeding rate. Of these two subjects, one experienced one bleeding episode over 91 days, and the other experienced no bleeding episodes over 123 days. Overall, the impact of the early withdrawals was minimal.

6.1.12 Safety Analyses

Per discussion with the clinical reviewer, the safety evaluation revealed that rFIXFc was well tolerated overall with no major concerns regarding the safety of rFIXFc.
The Safety Analysis Set included 123 subjects who received at least 1 dose of BeneFIX or rFIXFc. No subject developed an inhibitor, as assessed by a ---------(b)(4)---------- Bethesda assay. More than 100 subjects were assessed for at least 39 weeks of treatment, with more than 50 of those subjects on treatment for at least 1 year. A total of 60 subjects achieved at least 50 EDs, meeting the exposure requirement for assessment of inhibitor risk. There were no deaths reported during the conduct of the study.
Of the 123 subjects, 16 subjects (13.0%) reported at least 1 SAE with a total of 21 serious adverse events (SAEs). One subject experienced a SAE of obstructive uropathy [Investigator term: renal clot colic, not vascular] that was assessed by the Investigator as possibly related to the rFIXFc treatment.
Of the 123 subjects, 94 subjects (76.4%) reported at least 1 AE with a total of 320 AEs. Ten subjects (8.1%) experienced at least 1 AE that was assessed by the Investigator as related or possibly related to the rFIXFc treatment. Two subjects (1.6%) discontinued rFIXFc treatment due to an AE: 1 subject in Arm 1 had a device (endoprosthesis) related infection, and the other in Arm 3 had a road traffic accident. In both of these cases, the underlying reason for discontinuation of rFIXFc treatment and withdrawal from the study was that hospitalization occurred in a country where the study treatment could not be imported. Overall, the incidence of AEs was similar across Arms 1, 2, and 3 with 45 subjects (71.4%) in Arm 1, 23 subjects (79.3%) in Arm 2, and 20 subjects (74.1%) in Arm 3 reporting at least 1 AE. The percentage of subjects who experienced at least 1 AE was similar across the age subgroups 8 (72.7%) of 11 subjects in the adolescent subgroup (age 12-17) experienced 23 AEs, 78 (73.6%) of 106 subjects in the adult
Subgroup (age 18-64) experienced 250 AEs, and 2 subjects (100.0%) in the elderly subgroup (age 65 above). The type of AEs in each age subgroup appeared typical for that age population.

10. Conclusions

10.1 Statistical Issues and Collective Evidence

There is no statistical concern in the current submission.

10.2 Conclusions and Recommendations

The primary efficacy endpoint was a comparison of annualized bleeding rates between each of two prophylaxis arms and the on demand treatment arm. There was a statistically significant reduction in the estimated annualized bleeding rate for subjects in both prophylactic arms with an 83% reduction in annualized bleeding rate for the weekly prophylaxis regimen (Arm 1) and an 87% reduction for the individualized interval prophylaxis regimen (Arm 2) compared with on demand treatment (Arm 3). The safety evaluation revealed that no subject developed an inhibitor. The primary efficacy endpoint analysis provides adequate evidence to support the claims proposed in the BLA.