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Applicant	Biogen Idec, Inc.
Established Name	rFVIII Fc
(Proposed) Trade Name	ELOCTATE
Indication(s) and Intended Population(s)	Treatment of adults and children with hemophilia A for the following indications: control and prevention of bleeding episodes; routine prophylaxis to prevent or reduce frequency of bleeding episodes; and perioperative management (surgical prophylaxis).

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GLOSSARY

BLA	biologics license application
DNAUC	dose-normalized area under the curve
ED	exposure days
EDR	electronic data room
EPD	electronic patient diary
FAS	full analysis set
FcRn	Fc receptor
FVIII	factor VIII
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
IgG	immunoglobulin G
IgG1	immunoglobulin G1
IXRS	instant voice/web recognition system
PK	pharmacokinetics
PKAS	pharmacokinetic analysis set
PTPs	previously treated patients
rFVIII-Fc	recombinant coagulation factor VIII Fc fusion protein
---b(4)-----	
---b(4)-----	
Tmax	maximum activity
Vd	volume of distribution

1. Executive Summary

The applicant submitted a biologics license application for recombinant coagulation factor VIII Fc fusion protein (rFVIII-Fc) for the indication of treatment of hemophilia A. There was a statistically significant reduction in the estimated annualized bleeding rate for subjects in both prophylactic arms with a 92% reduction in annualized bleeding rate for the individualized prophylaxis regimen (Arm 1) and a 76% reduction for the weekly 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. The primary efficacy endpoint analysis provides adequate evidence to support the claims proposed in the BLA.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia A is an X-linked bleeding disorder that occurs predominantly in males and is characterized by deficiency of functional factor VIII (FVIII). The worldwide incidence of hemophilia A is approximately 1 case per 5000 male births. Numerous mutations that cause hemophilia have been identified. The F8 gene is one of the most complex genes in the genome. Individuals with severe hemophilia experience frequent and recurrent spontaneous or traumatic bleeding into the soft tissue and joints, leading to arthropathy,

muscle contractures, and severe disability. Signs and symptoms include joint swelling, joint and muscle pain, as well as mucosal and gastrointestinal tract bleeding.

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

There is no currently available cure for hemophilia A, and the treatment focuses on factor replacement therapy with plasma-derived or recombinant FVIII products to promote clotting. rFVIII-Fc is a recombinant fusion protein consisting of a single molecule of B-domain deleted human coagulation FVIII covalently attached to the Fc domain of human immunoglobulin G1 (IgG1). This type of construct has been termed a monomeric Fc fusion protein. The Fc enables binding to the neonatal Fc receptor (FcRn), which is responsible for protecting immunoglobulin G (IgG) from degradation and confers IgG the long half-life observed in humans. The FcRn is present in humans throughout life and protects IgG from catabolism. rFVIII-Fc was designed to offer a longer circulating half-life than currently available FVIII products, aiming to provide hemophilia A patients with prolonged protection and prevention of bleeding with less frequent dosing in a prophylaxis regimen.

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

A pre-BLA meeting on 02 August 2012 included a discussion on a revised statistical analysis plan, clinical study report of 997HA301 and a summary of Phase 1/2a and Phase 3 study data. FDA accepted the proposed statistical approach for analysis of the primary efficacy endpoints and the proposed presentation of electronic data in CDISC format for the Phase 3 study and in legacy format for the Phase 1/2a study. FDA also commented that pooling the Phase 1/2a and Phase 3 study data would not contribute significantly to the overall safety and efficacy profile, and an Integrated Summary of Efficacy and Integrated Summary of Safety are not required.

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.

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

All data sources are included in the applicant'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 998HA101; completed phase 3 study 997HA301; ongoing pediatric study 8HA02PED and ongoing study 8HA01EXT which is an extension to both the Phase 3 study (997HA301) and the pediatric study (8HA02PED). For details of each study refer to Section 5.3. While PK

data from the Phase 1/2a and Phase 3 studies were pooled for a population PK analysis, no efficacy data were collected in the single-dose Phase 1/2a study. Safety data from each study have been summarized separately and the comprehensive safety assessment in the Phase 3 study forms the primary basis for support of the marketing authorization application. Per discussion with the primary clinical reviewer, this review memo only focuses on the analysis of the primary endpoints and one of the secondary endpoints in the completed pivotal phase 3 study 997HA301. This reviewer also defers to the clinical reviewer and the PK reviewer for the analysis of PK parameters.

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

The study report 997HA301 (module 5.3.5.2) was reviewed and data files adbl.xpt, adsl.xpt, dm.xpt (module 5.3.5.2) were used for the verification of the analysis results discussed in this review memo.

5.3 Summaries of Studies/Clinical Trials

The following studies are included in the submission:

Completed Studies:

(1) Study 998HA101 (referred to as the “Phase 1/2a study”) was a Phase 1/2a open-label, multicenter, single-dose, dose-escalation study investigating rFVIII-Fc in 16 male, previously treated patients (PTPs) with severe hemophilia A (defined as <1 IU/dL [$<1\%$] endogenous FVIII). Eligible subjects were 12 years of age or older, with at least 100 prior exposure days (EDs) to a FVIII product.

(2) Study 997HA301 was a Phase 3, open-label, partially randomized, multicenter study that evaluated the safety, PK, and efficacy of rFVIII-Fc administered as an IV injection to 165 male subjects with severe hemophilia A (defined as <1 IU/dL [$<1\%$] endogenous FVIII), who were ≥ 12 years of age and had at least 150 prior EDs to a concentrate or recombinant coagulation FVIII (rFVIII) product. The study compared the annualized bleeding rate between subjects receiving an individualized (tailored) prophylaxis regimen or weekly prophylaxis regimen versus subjects on episodic (on-demand) dosing. Hemostatic response to rFVIII-Fc during surgery and throughout the perioperative period was also evaluated.

Ongoing Studies:

(3) Study 8HA02PED (referred to as “the pediatric study”) is an open-label, multicenter study evaluating the safety, PK, and efficacy of rFVIII-Fc in previously treated pediatric subjects with severe hemophilia A, who are <12 years of age, and have at least 50 EDs to FVIII products prior to enrollment. Approximately 50 male subjects (25 subjects <6 years of age and 25 subjects six to <12 years of age) are planned to complete at least 26 weeks of prophylactic treatment to attain at least 50 EDs.

(4) Study 8HA01EXT (referred to as “the extension study”) is an open-label, multicenter extension to both the Phase 3 study (997HA301) and the pediatric study

(8HA02PED). The extension study is evaluating the long-term safety and efficacy of rFVIII-Fc for prophylaxis and episodic treatment of bleeding episodes in PTPs with hemophilia A.

This review memo only focuses on the analysis of the primary endpoints of the completed pivotal phase 3 study 997HA301.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study 997HA301

6.1.1 Objectives

In a population of subjects with severe hemophilia A, the primary objectives of the study were:

- To evaluate the safety and tolerability of rFVIII-Fc administered as a prophylaxis, weekly, on-demand, and surgical treatment regimen (i.e., individualized prophylaxis [Arm 1], weekly prophylaxis [Arm 2], episodic dosing [Arm 3], and perioperative management)
- To evaluate the efficacy of the rFVIII-Fc tailored prophylaxis regimen (Arm 1) [i.e., individualized prophylaxis]
- To evaluate the efficacy of rFVIII-Fc administered as an on-demand (Arm 3) and surgical treatment regimen (i.e., episodic dosing and perioperative management)

Secondary objectives of this study in this study population were:

- To characterize the PK profile of rFVIII-Fc and compare the PK of rFVIII-Fc with the currently marketed product, Advate
- To characterize the range of dose and schedules required to adequately prevent bleeding in a prophylaxis regimen (i.e., individualized prophylaxis and weekly prophylaxis); maintain hemostasis in a surgical setting (i.e., perioperative management); or to treat bleeding episodes in an on-demand, weekly treatment, or prophylaxis setting (i.e., episodic dosing, weekly prophylaxis, or individualized prophylaxis)

6.1.2 Design Overview

This was a multicenter, open-label study to evaluate the safety, PK, and efficacy of rFVIII-Fc administered as an IV injection to subjects with severe hemophilia A (defined as <1 IU/dL [$<1\%$] endogenous FVIII) who were ≥ 12 years of age and had at least 150 prior exposure days (EDs) to any FVIII product. A schematic of the study design and treatments is presented in Figure 1.

Arm 1, Individualized (Tailored) Prophylaxis

Initial twice weekly dosing with 25 IU/kg of rFVIII-Fc on Day one and 50 IU/kg on Day four, followed by individualized dose and interval modification within the range of 25 to 65 IU/kg every three to five days to maintain a trough level of 1% to 3% (or higher, as clinically indicated) rFVIII-Fc activity. A total of 117 subjects received an individualized

regimen of rFVIIIc starting with a twice weekly regimen consisting of 25 IU/kg on the first day followed by 50 IU/kg on the fourth day. The dose and interval were adjusted within the range of 25-65 IU/kg every 3-5 days to maintain trough levels between 1 and 3% above baseline, or higher as clinically indicated to prevent bleeding. The median dosing interval was 3.5 days and the final median weekly dose for subjects on study for at least 6 months was 51 IU/kg, which supports the labeled dosing regimen. Among the 112 subjects treated for at least 6 months, 111 (99%) achieved a dosing interval of three days or longer, 39 (35%) achieved a dosing interval of 4 days or longer, and 33 (29%) achieved a dosing interval of 5 days or longer during the last 3 months on study.

Arm 2, Weekly Prophylaxis

65 IU/kg rFVIIIc every 7 days. Of the 24 subjects enrolled in the weekly prophylaxis arm, 23 received 65 IU/kg of rFVIIIc once weekly for a median period of 28 weeks.

Arm 3, Episodic (On-Demand) Dosing

Initial single dose of 50 IU/kg rFVIIIc followed by 10 to 50 IU/kg rFVIIIc, as required to treat a bleeding episode.

Subjects who were on a prophylaxis regimen prior to study entry were to enter Arm 1; subjects who were on an episodic regimen prior to study entry were to have the option to enter into Arm 1 or to be randomized into either Arm 2 or 3. Stratified randomization into Arm 2 or 3 was to occur based on individual annualized bleeding episodes in the past 12 months. Twenty-three subjects out of xx subjects received episodic (on-demand) doses for the treatment of bleeding episodes and were on study for a median period of 29 weeks.

Subgroups

Arm1 Sequential PK subgroup

A minimum of 16 subjects in Arm 1 were to be enrolled in the sequential PK subgroup at selected sites. Prior to the initial PK sampling, all subjects will undergo a washout of FVIII-containing products of at least 96 hours. PK assessments will be conducted on varying schedules, according to subjects' group assignments. All subjects will undergo rFVIIIc PK sampling at rFVIIIc Day 0 and peak measurement sampling at all scheduled visits subsequent to rFVIIIc Day 0. Subjects in Arms 1 and 2 will also have trough measurements at these visits. A subgroup of subjects will also undergo 3 days of PK profiling with a single dose of the comparator, Advate, beginning at Advate Day 0 before the rFVIIIc PK sampling and a repeat rFVIIIc PK sampling at 12 to 24 weeks after rFVIIIc Day 0. For subjects in all arms at selected sites, samples for -----b(4)----- will be collected coincident with PK profiling sampling timepoints according to the subjects' group assignments and evaluated by an exploratory -b(4)- performed at a central laboratory. Dependent upon the selected sites' testing capabilities, other exploratory global hemostasis assays, such as ----b(4)-----, will be assessed in a subset of study subjects, with samples collected at selected PK sampling timepoints. Data from the sequential PK subgroup were used for (1) the estimation of the terminal half-life for rFVIIIc and (2) the comparison between the PK profile of

rFVIIIIFc and that of Advate. There were 30 subjects enrolled in the sequential PK subgroup.

Arms 1, 2, and 3 – Perioperative Management (Surgery) Subgroup

Subjects from any arm who were to have major surgery during the study were to be considered for enrollment in the perioperative management subgroup provided they met the inclusion criteria for the subgroup. A minimum of 10 major surgeries in at least 5 subjects were to be evaluated in the study. Major surgery is defined as any surgical procedure (elective or emergent) that involves general anesthesia and/or respiratory assistance in which a major body cavity is penetrated and exposed, or for which a substantial impairment of physical or physiological functions is produced (e.g., laparotomy, thoracotomy, craniotomy, joint replacement, or limb amputation). Minor surgery is defined as any surgical procedure (elective or emergent) that does not involve general anesthesia and/or respiratory assistance (e.g., minor dental extractions, incision, and drainage of abscess, or simple excisions).

Subjects from any arm who have pre-planned major surgery may be considered for enrollment in this subgroup if they meet the following criteria:

1. Were to have major surgery
2. Had at least 12 rFVIIIIFc EDs
3. Had a negative inhibitor test result following at least 12 rFVIIIIFc EDs and within 4 weeks prior to surgery
4. Had completed, as a minimum, abbreviated PK sampling (up to 96 hours) obtained with rFVIIIIFc at a dose of 50 or 65 IU/kg

In addition:

Subjects who required emergency major surgery were eligible to receive rFVIIIIFc if:

1. The surgery occurred within the same institution with which the Investigator was affiliated or a study specific contract/agreement was in place with the separate institution
2. The Investigator was available for consultancy through the intra-operative period.

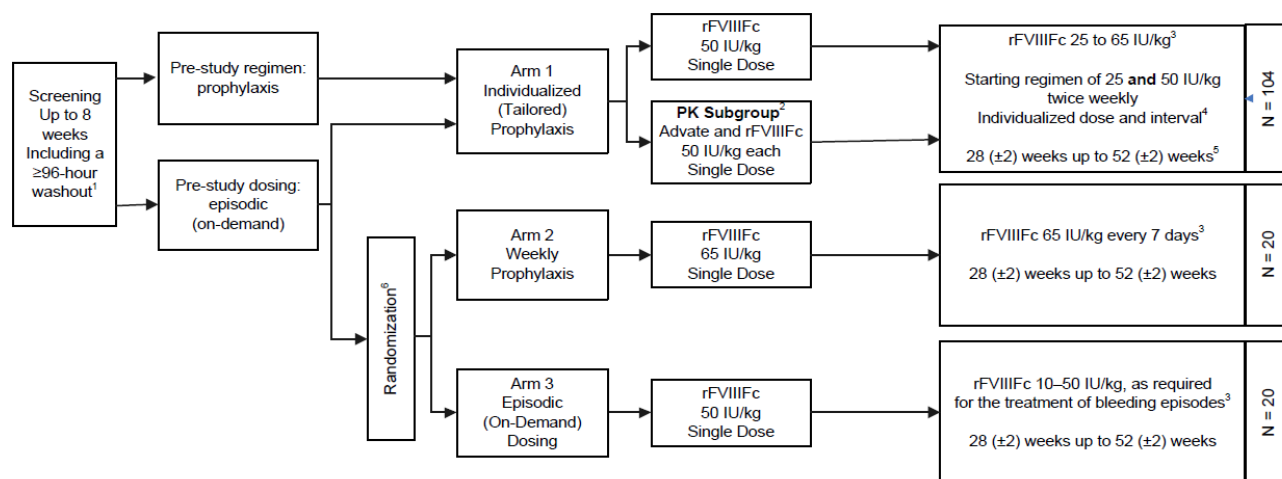
Subjects with planned surgery and participating in the sequential PK subgroup were not to enter the perioperative management subgroup until repeat PK sampling was completed 12 to 24 weeks following the rFVIIIIFc Day 0 PK profiling.

Dosing for any given subject was dependent on the type of surgery. If dosing continues for weeks (e.g., postoperative rehabilitation), the dose of rFVIIIIFc was to be adjusted to achieve a FVIII trough at a sufficient level to maintain hemostasis during the postoperative rehabilitation period, including adequate coverage for physical therapy. Subjects were to remain on the dose and schedule prescribed for the postoperative surgical prophylaxis until the Investigator deemed that it was safe for the subject to return to their previous treatment arm (Arm 1, 2, or 3). Subjects who underwent major surgery within 2 weeks before the end of study were to have their end of study visit performed no earlier than 14 days after surgery. There were nine subjects (eight subjects from Arm 1 and 1 subject from Arm 2) comprised the perioperative management subgroup. Nine major surgical procedures (2 laparoscopic inguinal hernia repairs, 5 knee surgeries,

appendectomy, and arthroscopy) were performed in those subjects. The median pre-operative dose was 51 IU/kg (range 50-77). The total dose on the day of surgery ranged from 66 to 115 IU/kg.

Statistical Reviewer Comment: *The study is not a real randomized clinical study. Only subjects who were on an episodic regimen before the enrollment of the study were randomized. The subjects who were on a prophylaxis regimen prior to the study entry will not be randomized, but instead be automatically assigned to Arm 1. This could result in an unbalanced prior study baseline treatment among different arms, and potentially bring bias to the study analysis result. In later section of this review memo, the subgroup analysis for subjects whose most recent pre-study regimen was episodic prior to the study start demonstrated a consistent analysis result.*

Figure 1. Study 997HA301 Design



6.1.3 Population

Candidates were required to have met the following criteria at Screening and prior to dosing:

Day 0 (rFVIIIc or Advate) to be eligible for the study:

1. Provided written informed consent and any authorizations required by local law (e.g., Protected Health Information). Parental or guardian consent was to be provided for subjects who were less than 18 years of age (or as per local regulations). Subjects less than 18 years of age (or as per local regulations) were to consent to the study by providing a signed assent form, if required by local regulations.
2. Male, 12 years of age or older, and weighing at least 40 kg
3. Have severe hemophilia A, defined as <1 IU/dL (<1%) endogenous FVIII, as determined by one-stage clotting assay from the central laboratory at the time of

screening. If the screening result was $\geq 1\%$, then the severity of hemophilia A could be confirmed by documented historical evidence from a certified clinical laboratory demonstrating $<1\%$ FVIII:C, as determined by the one-stage clotting assay from the medical record or from a documented genotype known to produce severe hemophilia A.

4. Previously treated subject, defined as having at least 150 documented prior EDs to any recombinant and/or plasma-derived FVIII and/or cryoprecipitate products at Day 0 (Advate or rFVIII-Fc). Fresh frozen plasma treatment was not to be considered in the count for the documented EDs.

5. No measurable inhibitor activity in two consecutive samples and absence of clinical signs or symptoms of decreased response to FVIII administration. (A historical first negative sample was permitted, if obtained within 12 weeks prior to screening. The second confirmatory sample was required in all cases to be performed by the central laboratory using the ---b(4)----- Bethesda assay. If no recent sample was available, then two negative samples at least one week apart and analyzed by the central laboratory using the ---b(4)----- Bethesda assay was to be obtained during screening.)

6. History of bleeding events and/or treatment with FVIII during the prior 12 weeks, as documented in the subjects' medical records

7. Willingness and ability of the subject or a surrogate (a caregiver or a family member ≥ 18 years of age) to complete training in the use of the study electronic patient diary (EPD) and to use the EPD throughout the study

8. For subjects entering Arm 1: Currently on a prophylaxis regimen at least two times per week with a FVIII product or on an on-demand (episodic) regimen with ≥ 12 bleeding episodes in the 12 months prior to Day 0 (Advate or rFVIII-Fc)

9. For subjects entering Arms 2 or 3: Currently on an on-demand (episodic) regimen with ≥ 12 bleeding episodes in the 12 months prior to Day 0 (rFVIII-Fc)

The following inclusion criterion refers to tests by the central laboratory sampled at screening and reviewed prior to Day 0 (Advate or rFVIII-Fc):

10. Platelet count $\geq 100,000$ cells/ μ L

The following inclusion criteria refer to tests performed within 6 months prior to screening. If not available, the test was to be conducted by the central laboratory, sampled at screening, and reviewed prior to Day 0 (Advate or rFVIII-Fc):

11. CD4 lymphocytes >200 mm³, if known as human immunodeficiency virus (HIV) antibody positive

12. Viral load of 400 copies/mL, if known as HIV antibody positive

6.1.6 Sites and Centers

A total of 165 male subjects were enrolled at 60 investigational sites in 19 countries worldwide. The highest enrolling countries were the United States (54 subjects), United Kingdom (20 subjects), South Africa (17 subjects), India (15 subjects), and Japan (14 subjects).

6.1.8 Endpoints

Primary Endpoints

The primary efficacy endpoint is:

- Annualized number of bleeding episodes (spontaneous and traumatic) Arm 1 versus Arm 3. A bleeding episode treated more than 72 hours after the last dose of the study drug to treat bleeding in the same location was considered a new bleeding episode. Bleeds that occur simultaneously on one subject but in different locations will be considered as separate bleeds.
- Primary PK parameters were the following assessments of FVIII activity: dose-normalized area under the curve (DNAUC), half-life ($t_{1/2}$), MRT, CL, and incremental recovery based on the one-stage clotting assay.

Safety and tolerability endpoints include:

- Clinically notable changes from baseline in physical examinations and vital signs
- Incidence of AEs, including clinically significant abnormal laboratory values
- Incidence of inhibitor development using the ---b(4)----- Bethesda assay

Secondary Endpoints

Overall

- Annualized number of bleeding episodes (spontaneous and traumatic) Arm 2 versus Arm 3
- Total annualized rFVIII Fc consumption per subject
- Subjects' individual assessments of response to treatment with rFVIII Fc for bleeding episodes, using a bleeding response scale
- Investigators' assessment of subjects' response to treatment with rFVIII Fc for bleeding episodes treated in the clinic, using a bleeding response scale
- Annualized number of spontaneous bleeding episodes (joint, soft tissue, and muscle) per subject
- Annualized number of joint bleeding episodes (spontaneous and traumatic) per subject
- Time from last injection of rFVIII Fc to a bleeding episode
- Number of injections and dose per injection of rFVIII Fc required to resolve a bleeding episode (joint, soft tissue, and muscle)
- Additional parameters for PK assessments were to include but not be limited to: DNAUC, half-life, MRT, CL, and incremental recovery based on the two-stage chromogenic assay; volume of distribution (Vd), time at maximum activity

(Tmax); and percent recovery for FVIII activity based on both the one-stage clotting assay and the two-stage chromogenic assay.

- QoL via hemophilia-specific health-related quality of life (HRQoL) questionnaire for children and parents or hemophilia-specific HRQoL questionnaire for adults (Haem-A-QoL; for ages 17 years and above)

Perioperative Management Subgroup

- Investigator's/Surgeon's assessments of subjects' response to surgery with rFVIII-Fc, using a bleeding response scale
- Number of injections and dose per injection required to maintain hemostasis during the surgical period
- Estimated blood loss during surgery
- Number and type of blood component transfusions required during surgery

Exploratory Endpoints

- Investigators' global assessment of subjects' response to treatment with rFVIII-Fc
- Health assessment via European Quality of Life-5 Dimensions (EQ-5D) for all subjects
- Health-economic parameters to include, but not be limited to, collection of information on the following:
 - Number of hospitalizations (excluding preplanned hospitalizations documented at screening)
 - Number of hospitalization days
 - Number of emergency room visits
 - Number of physician visits, excluding study visits
 - Number of days off school or work
- Global hemostasis assays dependent upon the selected sites' testing capabilities, including ---b(4)-----), and, for a subset of subjects, ---b(4)-----

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 (April 2, 2012):

Primary Efficacy Endpoint Analysis:

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

$$\text{Annualized bleeding rate} = \frac{\text{Number of bleeding episodes during the efficacy period}}{\text{Total number of days during the efficacy period}} \times 365.25$$

The annualized number of bleeding episodes was compared between the specified study arms using a Poisson regression model followed by a test for overdispersion. Due to the existence of overdispersion, the annualized bleeding rate was analyzed using negative

binomial regression. Statistical significance was controlled at the 2-sided 0.05 level, and the estimated ratio of annualized bleeding episodes (tailored prophylaxis: on-demand) was compared to 0.5 (i.e., greater than a 50% reduction). The time that each subject stayed on the efficacy study was included as an offset in the analysis of the annualized bleeding rate.

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 ($<80\%$, $\geq 80\%$, Arms 1 and 2), by the prophylactic dosing interval compliance rate ($<80\%$, $\geq 80\%$, Arms 1 and 2), and by the overall prophylactic dose and dosing interval compliance rate ($<80\%$, $\geq 80\%$, 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, \leq median of the number present, $>$ median of the number present)
- by age (12-17 years, 18-64 years, 65 years and older)

Safety Endpoint Analysis:

Safety analysis is based on descriptive statistics. No statistical hypothesis testing was performed and only the Clopper Pearson confidence interval was calculated for incidence of the inhibitor.

Study Sample Size:

Because of the limited number of subjects with severe hemophilia A, the sample size was based on clinical rather than statistical considerations. Taking into account the CPMP Note for Guidance [EMA 2000], the CHMP Guidance 2009 [EMA 2011], and in an effort to enroll a sufficient number of subjects to assess the efficacy and safety of rFVIII-Fc, approximately 144 subjects were planned to be enrolled into 3 treatment arms per the designed allocation.

Randomization

Subjects who were on a prophylaxis regimen prior to study entry were to enter into Arm 1 (individualized prophylaxis); subjects who were on an episodic regimen were to have the option to enter Arm 1 or to be randomized into either Arm 2 (weekly prophylaxis) or Arm 3 (episodic dosing). Randomization into Arms 2 or 3 was stratified based on the

number of bleeding episodes reported by the subject during the 12 months prior to screening in a ratio of 1:1 within a block size of 4. The randomization strata were:

- 12 to 20 bleeding episodes per year
- 21 to 50 bleeding episodes per year
- >50 bleeding episodes per year

Missing Data:

No imputation due to missing data was applied for analyses of efficacy endpoints. For Haemo-QoL, Haem-A-QoL and EQ-5D questionnaires, if a subject had data missing at a particular visit for a domain, the total score was estimated provided the minimum number of questions needed to calculate an overall score had been answered. If a subject's data could not be used to calculate an overall score, that subject was also excluded from summaries of individual domains at that visit and was flagged as excluded from summaries in the analysis dataset.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

All-Enrolled Analysis Set

The All-Enrolled Analysis Set will consist of subjects who have been registered as enrolled by instant voice/web recognition system (IXRS) and assigned a unique subject identification number.

Full Analysis Set (FAS)

The FAS is defined as all subjects who receive at least one dose of rFVIII-Fc. The analysis of efficacy will be performed in this population. Subjects who received a dose of Advate, but did not receive any rFVIII-Fc will not be included in this population.

Safety Analysis Set

The Safety Analysis Set is defined as all subjects who receive at least one dose of Advate or rFVIII-Fc. The analysis of safety will be performed in this population.

Pharmacokinetic Analysis Set (PKAS)

The PKAS was defined as all subjects in Arms 1, 2, or 3 who had completed evaluable sampling timepoints (through at least the 48-hour timepoint for the Advate profile or the 72-hour timepoint for the rFVIII-Fc PK profiling) to allow the acceptable determination of the terminal half-life.

Sequential PK Subgroup

The Sequential PK Subgroup was defined as subjects in Arm 1 who had evaluable PK profiles for both Advate and baseline rFVIII-Fc and/or evaluable PK profiles for both baseline rFVIII-Fc and the repeat rFVIII-Fc profile.

6.1.10.1.1 Demographics

The demographic factors of age, race, and geography were representative of the global hemophilia A population and were similar across all treatment arms. All subjects were

male. The median age was 30 years (range, 12 to 65 years), with 13 subjects (7.9%) 12 to 17 years old, 151 subjects (91.5 %) 18 to 64 years old, and 1 subject (0.6%) who was 65 years old. Of the subjects in the 12 to 17 years of age subgroup, all of whom were in either Arm 1 or Arm 3, one subject was 12 years old, two were 13 years old, three were 14 years old, two were 15 years old, four were 16 years old, and one was 17 years old. For the North America region, the average age is 32 for Arm 1, 42 for Arm 2 and 43 for the Arm 3. For the European region, the average age is 35 for Arm 1, 38 for Arm 2 and 37 for the Arm 3. For the other countries, the average age is 33 for Arm 1, 33 for Arm 2 and 30 for the Arm 3. Of the 165 subjects enrolled, 107 (64.8%) were white, 43 (26.1%) were Asian, 10 (6.1%) were black, and five (3.0%) were classified as other. The median weight was 71.6 kg (range, 42.0 to 127.4 kg), and median body mass index was 23.90 kg/m² (range, 15.3 to 37.4 kg/m²).

In general, the three main geographic regions were well represented in the study: Europe (24.8%), North America (33.9%), and other countries (41.2%). When each region was examined by treatment arm, the percentage of subjects from Europe was higher in Arm 1 (28.8%) relative to Arms 2 (12.5%) and 3 (17.4%). The higher proportion of subjects from Europe in Arm 1 is consistent with the more widespread use of prophylaxis in the treatment of hemophilia A in Europe, as subjects who entered the study on a prophylaxis regimen were eligible to participate only in Arm 1.

6.1.10.1.3 Subject Disposition

A total of 165 male subjects were enrolled at 60 investigational sites in 19 countries worldwide. The highest enrolling countries were the United States (54 subjects), United Kingdom (20 subjects), South Africa (17 subjects), India (15 subjects), and Japan (14 subjects). One hundred eighteen subjects participated in Arm 1 (individualized prophylaxis), 24 in Arm 2 (weekly prophylaxis), and 23 in Arm 3 (episodic [on-demand] dosing). Of the 118 subjects enrolled in Arm 1, 30 were enrolled in the sequential PK subgroup. Nine subjects (8 subjects from Arm 1 and 1 subject from Arm 2), comprised the perioperative management (surgery) subgroup.

A total of 153 subjects (92.7%) completed the study, and 12 subjects (7.3%) discontinued the study prematurely. The reasons for premature discontinuation were consent withdrawn (four subjects, 2.4%), other (three subjects, 1.8%), AEs (two subjects, 1.2%), physician decision (due to concerns about subject compliance) [two subjects, 1.2%], and death (one subject, 0.6%).

6.1.11 Efficacy Analyses

6.1.11.1 Primary Analyses of Efficacy Endpoint(s)

The annualized bleeding rate was analyzed using negative binomial regression. The estimated annualized bleeding rate was 2.91 (95% CI: 2.30, 3.68) for Arm 1, 8.92 (95% CI: 5.48, 14.51) for Arm 2, and 37.25 (95% CI: 24.03, 57.74) for Arm 3. The bleeding rate ratios obtained from the model were 0.08 (p<0.001) for Arm 1 versus Arm 3, and 0.24 (p<0.001) for Arm 2 versus Arm 3, indicating that the annualized bleeding rate was significantly reduced by 92% (Arm 1) and 76% (Arm 2) by using either the

individualized prophylaxis or weekly prophylaxis compared with episodic treatment. The analysis results show a statistically significant reduction in the annualized bleeding rate for both the individualized (tailored) prophylaxis (Arm 1) and the weekly prophylaxis (Arm 2) relative to episodic (on-demand) dosing (Arm 3).

Statistical Reviewer Comment: *The protocol stated that the data will be analyzed using Poisson regression model, but negative binomial model was used in the final study analysis due to overdispersion. This reviewer conducted a sensitivity analysis using the Poisson regression model and the results are consistent with the negative binomial model. Negative binomial model is a flexible model to analyze overdispersed data. When the overdispersion parameter in negative binomial model goes to infinity, the model turns to a Poisson model. In addition, existing literature considers Poisson regression with a correction of overdispersion is equivalent to negative binomial model (Hilbe 2011). The analysis conducted by the sponsor is acceptable.*

6.1.11.3 Subpopulation Analyses

The annualized bleeding rates were also analyzed for subjects whose most recent pre-study regimen was episodic prior to study start. The results demonstrate a reduction in bleeding for subjects on a prophylaxis regimen compared to subjects on an episodic regimen. Subjects were also grouped by frequency of prior bleeding episodes, and for all groups there was a lower annualized bleeding rate for subjects on a prophylaxis regimen relative to the episodic regimen.

Thirteen subjects aged 12 through 17 years (9% of Arm 1 and 9% of Arm 3), 149 subjects aged 18 through 64 years (90% of Arm 1, 96% of Arm 2, and 91% of Arm 3), and one subject aged ≥ 65 years (1% in Arm 1) contributed data in the efficacy period. For subjects aged 12 through 17 years, the median annualized bleeding rates were 1.92 and 28.85 (mean rates of 2.63 and 28.85) in Arms 1 and 3, respectively. For subjects aged 18 through 64 years, the median annualized bleeding rates were 1.44, 3.59, and 33.57 (mean rates of 2.88, 8.81, and 38.03) in Arms 1, 2, and 3, respectively.

The vast majority of sites (92%) enrolled five or less subjects, and none enrolled more than 13 subjects. Due to the rarity of the disease and the limited number of subjects per site, by-site analyses were not performed by the applicant.

Statistical Reviewer Comment: *This reviewer conducted a sensitivity analysis based on subjects only from the US region. Similar to the whole study population, the estimated annualized bleeding rate was 2.49 for Arm 1 (N=43), 8.50 for Arm 2 (N=4), and 32.25 for Arm 3 (N=7). The annualized bleeding rate of Arm 1 is statistically significantly different from Arm 3 at the significance level of 0.05 ($p < 0.001$) while the comparison between Arm 2 and Arm 3 resulted in a p-value of 0.08.*

6.1.11.4 Dropouts and/or Discontinuations

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

6.1.12 Safety Analyses

Overall, the safety profile of rFVIII^hFc was assessed in 164 subjects with exposure to rFVIII^hFc over a treatment period of up to 54 weeks and a follow-up period up to 30 days. No subject developed inhibitor and the inhibitor incidence rate for the confirmed cases was 0% (95% CI: 0%, 3.3%) based on a neutralizing antibody value ≥ 0.6 BU/mL in 110 subjects with ≥ 50 EDs and a valid inhibitor test (107 subjects on individualized prophylaxis, one subject on weekly prophylaxis, and two subjects on episodic dosing). The upper limit of 95% CI was below the generally used reference inhibitor rate (6.8%) in clinical trials.

There were no deaths related to rFVIII^hFc treatment. One death in Arm 1 was reported due to SAE of polysubstance overdose. Given the subject's past medical history, concomitant medications, and the nature of the event associated with this fatal outcome, the applicant is in agreement with the Investigator's assessment that the death of this subject is unrelated to rFVIII^hFc treatment. Overall, of the 164 subjects in Arms 1, 2, and 3, 12 subjects (7.3%) experienced at least 1 SAE with a total of 17 SAEs during the study (excluding SAEs reported during the perioperative management period). There were 15 treatment emergent SAEs reported from 10 subjects (8.5%) in Arm 1, two SAEs reported from two subjects (8.3%) in Arm 2, and no one (0%) in Arm 3 reported any SAE. None of the SAEs were assessed by the Investigator as related to the rFVIII^hFc treatment. The SAEs were as follows: injury, poisoning and procedural complications (face injury, femur fracture, and overdose); musculoskeletal and connective tissues disorders (back pain, haemarthrosis, lumbar spinal stenosis, and myalgia); gastrointestinal disorders (inguinal hernia and tooth disorder); nervous system disorders (restless legs syndrome and syncope); and other System Organ Class (SOC) (tachycardia, completed suicide, nephrolithiasis, respiratory distress, and hypertensive emergency).

Of the 164 subjects in the three arms combined, 108 subjects (65.9%) reported at least one AE in any SOC. The incidence of subjects reporting at least one AE was 68.4% (80 subjects) in Arm 1, 75.0% (18 subjects) in Arm 2, and 43.5% (10 subjects) in Arm 3. The SOC with AEs reported by the highest percentage of subjects was infections and infestations (43 subjects [26.2%]). The SOC with the next highest incidence was musculoskeletal and connective tissue disorders (31 subjects [18.9%]). Ten subjects (6.1%) experienced at least one AE that was assessed by the Investigator as related to rFVIII^hFc treatment (One event each in two subjects with missing relationship assessment data were counted as related). Of the ten subjects, five subjects (50%) are from Arm 1, three subjects (30%) are from Arm 2 and two subjects are from Arm 3 (20%).

Statistical Reviewer Comment: *Although none of the SAEs were assessed by the Investigator as related to the rFVIII^hFc treatment, it appears that there are higher SAEs and AEs incidence rates for Arm 1 and Arm 2 comparing to Arm 3. This could potentially due to the higher exposure days of Arm 1 and Arm 2 than Arm 3. This reviewer defers it to the clinical reviewer on the safety evaluation of the treatment.*

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 a 92% reduction in annualized bleeding rate for the individualized prophylaxis regimen (Arm 1) and a 76% reduction for the weekly 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.

REFERENCE

Joseph M. Hilbe. Negative Binomial Regression. Cambridge University Press, 2011.