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Application Type	Efficacy Supplement
STN	125487/99
CBER Received Date	March 13, 2015
PDUFA Goal Date	January 11, 2016
Division / Office	DHCR /OBRR
Priority Review	No
Reviewer Name(s)	Megha Kaushal
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Biogen Idec Inc.
Established Name	Antihemophilic Factor (Recombinant), Fc Fusion protein
(Proposed) Trade Name	Eloctate
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	<No Formulations>
Dosage Form(s) and Route(s) of Administration	Lyophilized Powder in single use vials containing nominally 250, 500, 750, 1000, 15000, 2000, or 3000 international units of Factor VIII.
Dosing Regimen	Routine prophylaxis: 50IU/kg every 4 days; adjusted based on patient response with dosing in the range of 25-65 IU/kg at 3-5 day intervals Dosing for on-demand bleeding episodes and peri-operative management: XXX
Indication(s) and Intended Population(s)	In adults and children with Hemophilia A for control and prevention of bleeding episodes; perioperative management; routine prophylaxis to prevent or reduce the frequency of bleeding episodes.
Orphan Designated (Yes/No)	Yes

TABLE OF CONTENTS

GLOSSARY

ABR	Annualized Bleeding Rate
ADR	Adverse Drug Reaction
BIMO	Bioresearch Monitoring
BLA	Biologics License Application
BU	Bethesda Unit
CI	Confidence Interval
eCTD	Electronic Common Technical Document
ED	Exposure Days
GCP	Good Clinical Practices
IgG1	Human Immunoglobulin G1
IU	International Units
PK	Pharmacokinetic
PTP	Previously Treated Patient
PUP	Previously Untreated Patient
PVP	Pharmacovigilance Plan
rFVIII	Recombinant Human FVIII
SAE	Serious Adverse Event

1. EXECUTIVE SUMMARY

STN 125487/99 is a biologics license application (BLA) efficacy supplement submitted by Biogen. This efficacy supplement includes the pediatric study data for recombinant Factor VIII Fc (rFVIIIFc), Eloctate, which was licensed in June 2014. This submission supports a labeling change based on additional final efficacy, pharmacokinetic (PK), and safety data regarding inhibitor development from the completed pediatric study and ongoing extension study.

Eloctate is a recombinant fusion protein consisting of a single molecule of B-domain deleted human coagulation Factor VIII (FVIII) covalently attached to the Fc domain of human immunoglobulin G1. The Fc enables binding to the neonatal Fc receptor (FcRn), which is responsible for protecting immunoglobulin G from degradation and protects IgG from catabolism offering a longer circulating half-life, providing hemophilia A patients with prolonged protection and prevention of bleeding. Eloctate has been licensed for the following indications including: control and prevention of bleeding episodes, perioperative management, and routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with Hemophilia A.

The pediatric study was an open label, multicenter evaluation of the safety, PK, and efficacy of Eloctate in pediatric previously treated patients (PTPs) with severe Hemophilia A. Subjects were <12 years of age at enrollment and had at least 50 EDs to recombinant or plasma derived FVIII products prior to enrollment.

The study's objective to support the current labeling changes was to evaluate the safety of Eloctate in PTPs with Hemophilia A by evaluating the occurrence of inhibitor development. There were 69 subjects exposed to Eloctate. There were no inhibitors reported for any of the 69 subjects in the full analysis set.

Secondary objectives included evaluating the efficacy of Eloctate for prevention and treatment of bleeding episodes; to evaluate and assess the PK of Eloctate; to evaluate Eloctate consumption for prevention and treatment of bleeding episodes. The total

annualized bleeding rate (ABR) was 1.96 with 25th and 75th percentiles (interquartile range [IQR]) of 0.0, 3.96. Overall, 32 subjects (46.4%) had no bleeding episodes reported during the efficacy period. Assessment of PK revealed 12.28 and 13.45 half-life for the <6 years of age cohort and 6 to<12 years of age cohort, respectively. Overall, 93% of bleeding episodes were controlled with ≤2 injections of Eloctate.

The results from this study suggest that Eloctate was well tolerated and effective for the control and prevention of bleeding when administered for routine prophylaxis using an individualized regimen. The prolonged half-life of Eloctate in pediatric subjects has the potential to reduce the dosing frequency for prophylaxis in pediatric patients with hemophilia A.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The purpose of this section is to summarize the demographic subgroup information in the applicant's pivotal studies, detailed elsewhere in the clinical review and in **lay terminology**. This section will be posted as a separate hyperlink for access by the public on the product's approval page in keeping with the FDASIA section 907 Action Plan (2014). Therefore terminology used should be comprehensible to the lay viewer but be scientifically accurate.
This section should include a breakdown of the participants in the clinical trial(s) by age, sex, race and/or ethnicity as it is provided by the sponsor. This may be accomplished through a narrative or graphically via a table or both. In addition, any statistically significant differences in effectiveness or safety and/or adverse events outcomes by subgroup via analysis by age, sex race and/or ethnicity provided either by the sponsor or through your review, should be summarized in lay terms in this section. If trends or signals are demonstrated without statistical significance, but may be scientifically useful, without being misleading in user decision making, these may be noted with appropriate qualification(s) with respect to sample size, statistical inference or amount of information available. If there was insufficient information to draw any conclusions, this should be stated. You should include any other qualifications that may be useful to maintain the accuracy of the information.

Demographics and Baseline Characteristics:

Demographics				
		<6 years old	6 to <12 years old	Total
	n	36	35	71
Age (years)	Mean ± SD	3.7 ± 1.1	8.1 ± 1.7	5.9 ± 2.6
Race (n, %)	White	24 (66.7%)	24 (68.6%)	48 (67.6%)
	Black	4 (11.1%)	5 (14.3%)	9 (12.7%)
	Asian	4 (11.1%)	1 (2.9%)	5 (7.0%)
Ethnicity (n, %)	Hispanic or Latino	1 (2.8%)	3 (8.6%)	4 (5.6%)

There were no American Indians, Native Alaskans, Hawaiian, or Pacific Islanders included in the study.

The limited sample size in blacks, asians, and hispanics makes it challenging to reach conclusions about the efficacy of Eloctate in these races and ethinicities. Since the predeliction for clinical bleeding is dependent on the degree of factor VIII deficiency, race

and ethnicity related differences in efficacy are expected to be minimal. Therefore, it is reasonable to extrapolate from Whites to the other races and ethnic groups.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia A is an X-linked congenital bleeding disorder caused by a deficiency of functional clotting factor VIII which manifests as bleeding episodes (BEs). It is the most common of the severe inherited coagulopathies with an incidence of approximately 1 in 10,000 births, with approximately 20,000 affected males in the United States. The relationship of bleeding severity correlates with clotting factor level. Patients with <0.01 IU/ mL or <1% of functional FVIII are categorized as severe with spontaneous bleeding into joints or muscles. Moderate severity and mild severity have clotting factor levels of 1-5% and 5 to<40%, respectively.

To prevent joint destruction, the standard of care for children with severe HA is primary prophylaxis with infusions of FVIII. These regular infusions are initiated at the time of the first bleeding episode in a joint or earlier aiming to prevent joint damage. However, inhibitory antibodies to infused FVIII products develop in a substantial percentage of patients treated with either plasma-derived or recombinant FVIII products, making usual treatment with FVIII complicated. Prophylaxis has been shown to prevent complications later in life and to decrease the incidence of inhibitor formation. Although regulatory decisions for approval of these products are generally based on studies in PTPs, the FDA evaluates the safety data from PUPs to assess the immunogenicity of these products.

There are currently over ten rFVIII products licensed for marketing, with Eloctate being the only Fc product. These products have been approved in adults and children with Hemophilia A for the control and prevention of bleeding episodes, perioperative management of bleeding, and routine prophylaxis to reduce the frequency of bleeding episodes and the risk of joint damage.

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

Treatments for Hemophilia A require replacement with a form of FVIII. Factor VIII treatments include human plasma derived and recombinant FVIII preparations which are the mainstay of therapy. FDA approved recombinant FVIII products include Helixate, Kogenate FS, Advate, Recombinate, Refacto, Xyntha, and Nuwiq. There are also multiple approved plasma derived FVIII products which include Alphanate, Humate and Hemofil.

2.3 Safety and Efficacy of Pharmacologically Related Products

Pathogen transmission and inhibitor formation are the main safety concerns when treating hemophilia patients with FVIII replacement therapy. The availability of recombinant FVIII products reduces the risk of pathogen transmission, but not inhibitor development.

Potential problems with these products, even the rFVIII products include the development of neutralizing antibodies (inhibitors) and the potential for allergic reactions to animal-based proteins remaining from the synthetic process. The development of inhibitors decreases the efficacy of replacement therapy, increases the risk of unmanageable bleeding and increases cost of treatment (by 3-5 fold)[1]. The incidence of inhibitor development is approximately 30% in severe disease and less in mild or moderate disease. The highest incidence is in previously untreated patients with severe disease (reported from 3-52%). Inhibitor development in previously treated patients is less, reported as 0.9-4%. Potential risk factors for inhibitor development include genetic factors such as the type of FVIII gene mutation, human leucocyte antigen (HLA) type, polymorphisms in immune regulatory regions, family history of inhibitors and ethnic background as well as immunologic environment during early treatment and high intensity of treatment (either peak acute treatment or high overall treatment frequency).

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Human experience with the product occurred for the first time with this product under the IND.

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

Clinical trials that provided the evidence for safety and efficacy of ELOCTATE™ were conducted under IND 14134. Please refer to the original BLA clinical memo for the summary of the regulatory action related to the submission. Postmarketing commitments were required to complete the data analysis for the pediatric trial, the extension study, and the study in previously untreated patients.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was organized to perform a complete clinical review without unreasonable difficulty. The submission consisted of five modules in the Common Technical Document Structure.

3.2 Compliance With Good Clinical Practices And Submission Integrity

CBER Bioresearch Monitoring issued inspection at the time of the original application. Please refer to original BLA memo for the details as pertaining to inspection outcomes.

In this pediatric study, there were 38 subjects with deviations that were considered major; 24 subjects had informed consent issues (not clinically meaningful), 2 subjects took excluded medication, and 22 subjects had deviations based on other criteria. Every deviation associated with the completion of the consent form was considered major, regardless of whether the deviation was considered to be clinically meaningful.

1) Goudemand J: hemophilia. Treatment of patients with inhibitors: cost issues. *Haemophilia* 2013;5:397-491.
Gringeri A, Mantovani LG, Scalone L, Mannucci PM: Cost of care and quality of life for patients with hemophilia complicated by inhibitors: the COCIS Study Group. *Blood* 2003; 102:2358-2363.

Of the 38 subjects with major protocol deviations, 2 subjects were identified as having deviations that were considered to have a potential impact on annualized bleeding rate. A sensitivity analysis excluding these subjects was performed in this study.

Reviewer Comment:
These major deviations did not affect the primary analysis, although a large percentage (55.1%) had a least one major deviation which were mostly due to issues with the informed consent. The other deviations were further categorized into IP compliance, study procedure criteria, administrative criteria, and "other" criteria.

3.3 Financial Disclosures

Covered clinical study (name and/or number):998HA101		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified:		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: 2		
Covered clinical study (name and/or number):8HA02PED		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 111		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value		

could be influenced by the outcome of the study: _____

Significant payments of other sorts:

Proprietary interest in the product tested held by investigator: _____

Significant equity interest held by investigator in sponsor of covered study:

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Please see CMC review memo from the original BLA for complete details.

Eloctate Antihemophilic Factor (Recombinant), Fc Fusion Protein is a sterile, non-pyrogenic, lyophilized powder for reconstitution for intravenous injection. The product is supplied in single use vials containing nominal potencies of 250, 500, 750, 1000, 1500, 2000 or 3000 international units (IU). Each vial of ELOCTATE™ is labeled with the actual content in IU. The powder for injection is reconstituted with 3 mL sterile water for injection (SWFI) supplied in a sterile pre-filled syringe. The reconstituted product contains the excipients: sucrose [redacted] sodium chloride, L-histidine, calcium chloride and polysorbate 20. Eloctate contains no preservatives. The active ingredient in Eloctate is a B-domain deleted, recombinant Factor VIII construct covalently linked to the dimeric Fc domain of IgG_1 [redacted]

4.2 Assay Validation

Please see CMC review memo from the original BLA for complete details.

4.3 Nonclinical Pharmacology/Toxicology

Please refer to the Pharmacology/Toxicology review memo from original BLA and this supplement for complete details.
The preclinical experience with Eloctate included using a mouse and dog model of Hemophilia A. Findings from these studies indicated that the coagulation defects were corrected and the terminal half-life of Eloctate was increased 2-fold compared to other Factor VIII products. Toxicology studies were in rats and monkeys. There were no adverse toxicological findings directly related to effects of Eloctate at the highest dose tested.

4.4 Clinical Pharmacology

Please refer to the Clinical Pharmacology review memo for complete details. The pediatric study evaluated the PK of Eloctate in pediatric PTPs with severe Hemophilia A. Sixty subjects were enrolled in the PK subgroup. A washout period with no FVIII treatment was required prior to administration of prestudy FVIII and prior to Eloctate. After completing PK assessments, 58 subjects began prophylactic treatment with Eloctate.

Fifty-one subjects from a total of 55 subjects who received their prior FVIII therapy at the baseline visit (5 subjects were exempt due to historical data) had analyzable PK profiles. There were 24 subjects in the <6 years of age cohort and 31 subjects in the 6 to <12

years of age cohort where PK endpoints were analyzed. Four PK profiles were excluded from the analysis due to missing/abnormal pre-dose activity. Fifty-one subjects had a complete and evaluable PK profile for prestudy FVIII and Eloctate.

4.4.1 Mechanism of Action

Eloctate is a recombinant fusion protein that temporarily replaces the missing Coagulation Factor VIII needed for effective hemostasis. Eloctate contains the Fc region of human immunoglobulin G_1 (IgG_1) that binds to neonatal Fc receptor (FcRn). This receptor is part of a naturally occurring pathway that protects immunoglobulins from lysosomal degradation by cycling them back into circulation, and prolonging their plasma half-life.

4.4.2 Human Pharmacodynamics (PD)

Please refer to the clinical pharmacology review for additional details.

4.4.3 Human Pharmacokinetics (PK)

PK profiles were determined by both one stage clotting and chromogenic substrate assays. In the Phase 1/2a study, two single doses were administered intravenously, either 25 IU/kg to six subjects or 65 IU/kg to nine subjects. The mean clearance values (mL/kg/h) were estimated as 1.72 for subjects receiving 25 IU/kg and 2.55 for subjects receiving 65 IU/kg. In the Phase 3, pivotal study, a PK subgroup of 28 subjects received a single dose of 50 IU/kg. The mean, incremental, *in vivo* recovery (IVR) was calculated as 2.26 IU/dL per IU/kg. Mean clearance was estimated to be 2.06 mL/h/kg. The terminal half-life of 19.7 hr. was consistent with results of the Phase 1/2a study. During repeated dosing, Eloctate PK profiles were comparable at week 14 with the PK profile obtained after the first dose. The PK profiles and estimated parameters for adolescents (12 to <18 years of age) were similar to adults.

The ongoing pediatric study has assessed PK profiles in 27 pediatric, previously treated patients (2 to <12 years of age) at a dose of 50 IU/kg. Although, no clinically relevant differences between adults and children 6 to 12 years of age were observed, there was a 58% relative increase in mean body weight adjusted clearance (CL). PK parameters were comparable whether derived from one stage clotting or chromogenic substrate assays.

PK Parameters	**Pediatric Study**	
	1 to 5 Years	**6 to 12 Years**
	N = 23	**N = 32**
Mean Incremental Recovery (IU/dL per IU/kg)	1.92 (1.80, 2.04)	2.44 (2.07, 2.80)
Mean AUC/Dose (IU x h/dL per IU/kg)	30.0 (26.5, 33.6)	41.9 (34.0, 49.8)

PK Parameters	Pediatric Study	
	1 to 5 Years	**6 to 12 Years**
	N = 23	**N = 32**
Mean $t_{½}$ (h)	12.7 (11.2, 14.1)	14.9 (12.0, 17.8)
Mean Clearance (mL/h/kg)	3.60 (3.13, 4.07)	2.78 (2.44, 3.13)
V_{ss} (mL/kg)	58.6 (54.9, 62.3)	52.1 (45.3, 59.0)

Reviewer Comment:
This difference in clearance should be taken into account when dosing children 2 to <6 years of age.

4.5 Statistical

Please refer to the Statistical Review Memo for complete details. Descriptive statistics were used in this supplement.

4.6 Pharmacovigilance

The analyses of the safety data did not identify safety issues in the use of Eloctate in pediatric PTPs with severe hemophilia.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The data used in the review of this BLA were based on the clinical data provided in BLA 125487 Supplement 99.

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

Documents pertinent to the review of this submission were provided in BLA 125487/99.

5.3 Table of Studies/Clinical Trials

The completed, in-progress, and planned clinical trials are summarized in the Tables below adapted from 125487/99.

Type of Study	Study Identifier	Study Objectives	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects Enrolled; Completed	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety, PK	998HA101	Assess the safety and PK of a single administration of rFVIIIFc at 2 dose levels (25 and 65 IU/kg)	Open-label, multicenter, dose escalation Active comparator (Advate®)	rFVIIIFc; Single dose at 1 of 2 levels: 25 or 65 IU/kg; IV	19; 16	Previously treated patients (PTPs) ≥12 years old with severe hemophilia A	1 day (single dose); 28-day follow-up	Complete; Full

Type of Study	Study Identifier	Study Objectives	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects Enrolled; Completed	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety, Efficacy, PK	997HA301	Evaluate the safety and tolerability of rFVIIIFc; Evaluate the efficacy of rFVIIIFc for individualized prophylaxis, weekly prophylaxis, episodic (on-demand) dosing, and perioperative management; Characterize the PK profile of rFVIIIFc and compare with that of Advate®; Characterize range of dose and schedules to adequately prevent bleeding in an individualized or weekly prophylaxis regimen; maintain hemostasis in a surgical setting; or treat bleeding episodes in an episodic dosing, weekly prophylaxis, or individualized prophylaxis setting	Open-label, multicenter, partially randomized; Uncontrolled, overall: active comparator (Advate®) for Arm 1 sequential PK subgroup	rFVIIIFc; **Arm 1 (individualized prophylaxis)**: Initial twice weekly dosing with 25 IU/kg of rFVIIIFc on Day 1 and 50 IU/kg on Day 4. Thereafter, 25 to 65 IU/kg every 3 to 5 days. (For **sequential PK subgroup**: a single dose of 50 IU/kg Advate as comparator for PK profiling.) **Arm 2 (weekly prophylaxis)**: 65 IU/kg of rFVIIIFc every 7 days **Arm 3 (episodic dosing)**: 10 to 50 IU/kg of rFVIIIFc, as required **Major surgery subgroup (subjects from Arms 1, 2, and 3)**: as required for perioperative management; IV	165; 153	PTPs ≥12 years old with severe hemophilia A	Up to 75 weeks for subjects in the sequential PK subgroup and up to 67 weeks for all other subjects for screening, treatment, and follow-up	Complete; Full
Safety, Efficacy, PK	8HA02PED	Evaluate safety, efficacy, and PK of rFVIIIFc in pediatric patients; Evaluate rFVIIIFc consumption; Evaluate the effect of rFVIIIFc based on patient-reported outcomes and health outcomes	Open-label, multicenter; Uncontrolled	rFVIIIFc; Twice weekly prophylaxis with initial doses of 25 IU/kg on Day 1 and 50 IU/kg on Day 4; thereafter the dosing regimen can be adjusted to 20 to 40 IU/kg for Day 1 and 40 to 60 IU/kg for Day 4, up to a maximum of 80 IU/kg every 3 days; IV	35 subjects <6 years of age and 34 subjects 6 to <12 years of age	PTPs <12 years old with severe hemophilia A	~28 weeks for treatment and follow-up periods (at least 50 EDs)	Complete; Full

Type of Study	Study Identifier	Study Objectives	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects Enrolled; Completed	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety, Efficacy	8HA01EXT	Evaluate the long-term safety and efficacy of rFVIIIFc	Open-label, multicenter, long-term extension study; Uncontrolled	rFVIIIFc; Episodic dosing: Dose based on subject's clinical condition and type and severity of bleeding event **Prophylaxis**: Individualized Prophylaxis: 25 to 65 IU/kg every 3 to 5 days, or 2 times per week at 20 to 65 IU/kg on Day 1 and 40 to 65 IU/kg on Day 4. In paediatric subjects, dose adjustments up to a maximum prophylactic dose of 80 IU/kg and frequency of administration up to every 2 days can be used if necessary; Weekly Prophylaxis: 65 IU/kg once weekly; For both prophylaxis regimens, Investigator may further modify dosing level or interval to meet the needs of individual subjects. **Surgery**: As required for perioperative management; IV	211 enrolled as of 06 Jan 2014; 0 completed	Adult and pediatric PTPs with severe hemophilia A who have completed Study 997HA301, Study 8HA02PED or any other study with rFVIIIFc	Up to 4 years or until rFVIIIFc is commercially available in participating countries	Ongoing; Interim
PK	997HA307	Characterise PK of rFVIIIFc at 2 vial strengths (1000 and 3000IU); Evaluate safety of rFVIIIFc	Phase I, multicenter, randomized, open-label, crossove	rFVIIIFc; For PK assessment, injection of rFVIIIFc 50 IU/kg at a strength of either 1000 or 3000 IU/vial then an additional injection 5 – 28 days later of rFVIIIFc 50 IU/kg at the other strength. Following the PK assessment, either an episodic (on-demand) regimen with doses between 20 and 50 IU/kg, or 1 of 2 prophylactic regimens: 50 IU/kg every 3 to 5 days or 65 IU/kg weekly, for up to 6 months; IV	12 planned; 5 enrolled as of 30th May 2014 (only 4 received both PK doses)	Previously treated patients ≥ 12 years old with severe haemophilia	Up to 6 months following PK assessments	Ongoing; Progress report

4

5.4 Consultations

No consultations were requested for the review of this efficacy supplement.

5.4.1 Advisory Committee Meeting (if applicable)

N/A

5.4.2 External Consults/Collaborations

N/A

5.5 Literature Reviewed (if applicable)

N/A

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1 (Study Number: 8HA02PED)

An Open-Label, Multicenter Evaluation of Safety, Pharmacokinetics, and Efficacy of Recombinant Coagulation Factor VIII Fc Fusion Protein, BIIB031, in the Prevention and Treatment of Bleeding Episodes in Pediatric Subjects With Hemophilia A

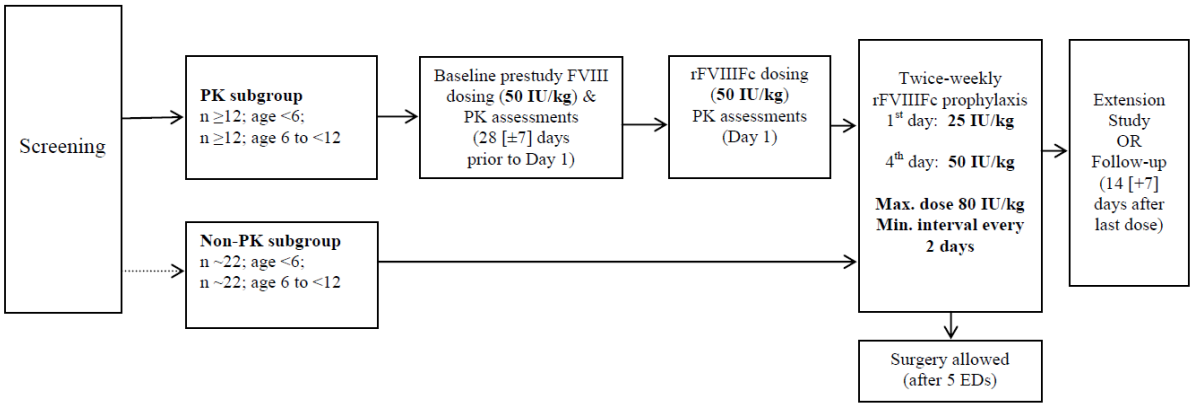
6.1.1 Objectives (Primary, Secondary, etc)

The primary objective of the study was to evaluate the safety of Eloctate in previously treated pediatric subjects with Hemophilia A.
The secondary objectives were the following:
-To evaluate the efficacy of Eloctate for prevention and treatment of bleeding episodes.
-To evaluate and assess the PK of Eloctate.
-To evaluate Eloctate consumption for prevention and treatment of bleeding episodes.

The exploratory objective was to evaluate the effect of Eloctate based on patient reported outcomes and health resource utilization.

6.1.2 Design Overview

The study was an open label, multicenter evaluation of the safety, PK, and efficacy of Eloctate in pediatric PTPs with severe Hemophilia A. Subjects were <12 years of age at enrollment and had at least 50 EDs to recombinant or plasma derived FVIII products prior to enrollment. The study recruitment target was for a minimum of 50 subjects (25 subjects who were <6 years of age and 25 subjects were 6 to<12 years of age) to complete approximately 26 weeks of treatment to obtain at least 50 EDs on study. The duration of time required for screening and PK assessments was approximately 12 weeks.



6.1.3 Population

To be eligible to participate in this study, the following inclusion criteria were required:

1. Ability of parent or legal guardian to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information in accordance with national and local subject privacy regulations. Subjects may have provided assent in addition to the parental/guardian consent, if appropriate.
2. Male, <12 years of age, and weight ≥13 kg.
3. Severe hemophilia A defined as <1 IU/dL (<1%) endogenous FVIII as documented in medical records from a local clinical laboratory demonstrating <1% FVIII:C or a documented genotype known to produce severe hemophilia A.
4. Previously treated subject, defined as having at least 50 EDs to any recombinant or plasma-derived FVIII product including cryoprecipitate (blood products including fresh frozen plasma treatment was not considered in the count of the documented EDs).
5. If known to be human immunodeficiency virus (HIV) positive, the following laboratory values were required, based on results within last 6 months:
-platelet count ≥100,000 plts/μL
-CD4 count ≥200 cells/μL
-viral load of <400 copies/mL
6. No history of, or currently detectable, inhibitor. This included the following:
- at least 2 negative inhibitor tests from the reporting laboratory
AND/OR
-normal recovery tests within the first 50 EDs to FVIII products
AND
-absence of clinical signs of decreased response to FVIII administrations
Historical positive inhibitor test was defined as per local laboratory Bethesda value for positive inhibitor test (i.e., equal to or above lower level of detection). Family history of inhibitors would not exclude the subject.
7. No measurable inhibitor activity using the (b) (4) Bethesda assay (≥0.6 BU/mL is considered positive) at Screening.
8. Willingness and ability of the subject's parent or legal guardian to complete training in the use of the study electronic patient diary (EPD) and to use the EPD throughout the study.

Subjects were excluded from the study if any of the following exclusion criteria existed at the time of screening:
1. Other coagulation disorder(s) in addition to hemophilia A.
2. History of anaphylaxis associated with any FVIII or IV immunoglobulin administration.
3. Active renal disease (per the discretion of the Investigator and medical records).
4. Active hepatic disease (per the discretion of the Investigator and medical records).
5. Any concurrent clinically significant major disease that, in the opinion of the Investigator would have made the subject unsuitable for enrollment.
6. Current systemic treatment with chemotherapy and/or other immunosuppressant drugs, with the following exceptions: use of steroids for treatment of asthma or management of acute allergic episodes, and routine immunizations.
7. Participation within the past 30 days in any other clinical study involving investigational drugs.
8. Surgery within 30 days prior to the Screening Visit (visit could be rescheduled and subject screened).

Reviewer Comment:
These inclusion and exclusion criteria are acceptable.

6.1.4 Study Treatments or Agents Mandated by the Protocol

PK subgroup:
A washout period for 72 hours was required prior to prestudy FVIII and Eloctate. At the baseline visit, subjects received a single IV dose of 50IU/kg of prestudy FVIII for PK sampling. A subsequent washout period of at least 72 hours was required prior to treatment with Eloctate for the PK assessment. The starting dose regimen was 25 IU/kg on Day 1 and 50 IU/kg on Day 4 and then administered twice weekly.

6.1.5 Directions for Use

Please refer to clinical review memo 125487/0.

6.1.6 Sites and Centers

There were 23 sites that were enrolled eligible subjects into this study. The sites that screened and enrolled subjects into this study were located in the following 8 countries: Australia, Hong Kong, Ireland, Netherlands, Poland, South Africa, United Kingdom, and the United States (US).

6.1.7 Surveillance/Monitoring

Please see the clinical review memo from the original BLA for complete details.

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint was inhibitor occurrence.

The secondary endpoints included the following:

- annualized number of bleeding episodes (spontaneous and traumatic) per subject
- annualized number of spontaneous joint bleeding episodes per subject
- assessments of response to treatment with Eloctate for bleeding episodes, using the 4-point bleeding response scale

Investigators recorded assessments of each subject's response to his assigned Eloctate regimen using the following 4-point scale:
Excellent: abrupt pain relief and/or improvement in bleeding; Good: definite pain relief and/or improvement in signs of bleeding but possibly requiring more than one injection; Moderate: probable beneficial effect and requiring more than one injection; No response: no improvement or condition worsens. Response evaluated at approximately 8-12 hours after treatment.

- total annualized Eloctate consumption per subject for the prevention and treatment of bleeding episodes
- time from the last injection of Eloctate to the bleeding episode
- number of injections and dose per injection of Eloctate required to resolve a bleeding episode

The PK endpoints included the following:

- maximum plasma activity (Cmax)
- terminal half-life ($t^{½}$)
- clearance (CL)
- volume of distribution at steady-state (V_{ss})
- dose-normalized area under the concentration-time curve (DNAUC)
- mean residence time (MRT)
- incremental recovery (IR, K-value)
- time to reach Cmax (Tmax)
- first order rate constant associated with the terminal portion of the curve (lambda z)
- time of the first data point used to determine t½ (lambda [lower])
- time of the last data point used to determine t½ (lambda [upper])
- volume of distribution estimated from the terminal phase (V_z)
- area under the concentration-time curve to the last measureable timepoint (AUC_{last})
- area under the concentration-time curve to infinity (AUC_{inf})
- percentage of AUC_{inf} extrapolated from the last data point to infinity ($\%AUC_{ext}$)

Exploratory Endpoints include:

- Patient Reported Outcome Endpoints
    - Canadian Hemophilia Outcomes-Kids' Life Assessment Tool (CHO-KLAT)
      -children
      -proxy version for parents
    - Hemo-Sat Patient Satisfaction Scale for parents
    - European Quality of Life-5 Dimensions Youth (EQ-5D-Y) for children
- Health outcome endpoints

Reviewer Comment:
These endpoints used in this study are consistent with the general approach to evaluation of this class of products.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Descriptive statistics were used throughout the study. The SAP was considered acceptable at the time of the original BLA submission.

6.1.10 Study Population and Disposition

PK subgroup:
The PK subgroup included 54 subjects from 2 age cohorts (23 subjects who were <6 years of age and 31 subjects who were 6 to <12 years of age). These subjects underwent an evaluation of the PK profile of prestudy FVIII and Eloctate sequentially and received PK assessments with both prestudy FVIII and Eloctate. A washout period with no FVIII treatment was required prior to administration of either product.
After results of the PK assessments, the remaining subjects had the option of proceeding directly to twice-weekly prophylactic treatment (starting dose regimen) or entering the PK subgroup. On Day 1, subjects were to receive a single IV injection of Eloctate at a dose of 25 IU/kg and a dose of 50 IU/kg on Day 4.

For those subjects treated for perioperative management, surgery was allowed only after at least 5EDs to Eloctate without safety concerns. If a major surgery was planned,

subjects from the non-PK group were required to have a PK assessment; this was not required for minor surgeries. The dose and interval of Eloctate was determined by PK. Unexpected bleeding was reported.

6.1.10.1 Populations Enrolled/Analyzed

A total of 71 male subjects were enrolled. Two subjects received prestudy FVIII but were not treated with Eloctate. Sixty nine subjects were enrolled in the efficacy cohort.

6.1.10.1.1 Demographics

The median overall age was 5.0 years (range, 1 to 11 years); in the <6 years of age cohort, the median age was 4.0 years (range, 1 to 5 years), and in the 6 to <12 years of age cohort, the median age was 8.0 years (range, 6 to 11 years). The predominant races represented in the study were white (67.6%) and black (12.7%). The main geographic areas represented were Europe (45.1%) and North America (28.2%); 26.8% of the study population was from other geographic areas, which included Australia, Hong Kong, and South Africa. The demographics and baseline characteristics of the PK analysis set are consistent with the characteristics of the overall study population as expected, since the PK analysis set comprises 55 of the 71 subjects (77.5%) in the study population.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Please see clinical review memo from the original BLA for complete details.

6.1.10.1.3 Subject Disposition

A total of 71 male subjects were enrolled. Sixty-nine subjects continued on with Eloctate prophylaxis dosing, of which seven subjects were on a prior episodic dosing and 62 subjects were on prior prophylaxis dosing. There were 67 subjects who completed the study. Two subjects received only the prestudy FVIII. Two subjects did not complete the study.

6.1.11 Efficacy Analyses

The primary efficacy endpoint was derived from laboratory evaluation. Secondary efficacy endpoints were derived from information recorded by the subject or the subjects' caregivers. There were 35 in the<6 years of age cohort and 34 in the 6 to <12 years of age cohort. Two subjects received only the prestudy FVIII.

6.1.11.1 Analyses of Primary Endpoint(s)

<u>Inhibitor development</u>
The test for inhibitors to Eloctate after 10 to 15 EDs was completed by 62 subjects. No inhibitor development was detected in these subjects.

Reviewer Comment:
Sixty one subjects had at least 50 EDs and had valid inhibitor testing, which met the exposure requirement for assessment of inhibitor risk. No subject developed an inhibitor.

6.1.11.2 Analyses of Secondary Endpoints

Annualized Bleeding Rate (ABR)

Results from the annualized bleeding rate was observed for both age cohorts (<6 years of age and 6 to <12 years of age, and total). The median ABR was 0.00 with 25 [h] and 75th percentiles of 0.0 and 3.96, respectively, in the <6 years age cohort. The median ABR was 2.01 with 25th and 75th percentiles of 0.0 and 4.04, respectively, in the 6 to <12 years age cohort, and the median ABR was 1.96 with 25th and 75th percentiles of 0.0 and 3.96, respectively, in the total cohort.

Thirty-two patients had no bleeding episodes during the efficacy period (18 subjects in <6 years of age and 14 subjects in the 6 to <12 years of age cohort). Two subjects (one in each age cohort) had >10 annualized bleeding episodes/year.

	Age cohort		
	<6 years old (N=35)	6 to <12 years old (N=34)	Total (N=69)
Annualized bleeding rate (Episodes/Year)			
0	18 (51.4%)	14 (41.2%)	32 (46.4%)
>0-5	10 (28.6%)	13 (38.2%)	23 (33.3%)
>5-10	6 (17.1%)	6 (17.6%)	12 (17.4%)
>10-20	1 (2.9%)	0	1 (1.4%)
>20	0	1 (2.9%)	1 (1.4%)
Annualized bleeding rate per subject			
n	35	34	69
Mean	2.25	2.99	2.62
SD	2.976	5.022	4.100
Median	0.00	2.01	1.96
25th, 75th percentile	0.00, 3.96	0.00, 4.04	0.00, 3.96
Min, Max	0.0, 10.5	0.0, 27.2	0.0, 27.2

Response to Treatment with Eloctate Injections for Bleeding Episodes

Overall, 89.4% injections were rated by subjects as producing an excellent or good response. 112 injections were used to treat 86 bleeding episodes and 104 were evaluated for response.

	Age cohort		
	<6 years old (N=35)	6 to <12 years old (N=34)	Total (N=69)
Each injection			
Based on injections with an evaluation			
n (a)	45	59	104
Excellent or Good	41 (91.1%)	52 (88.1%)	93 (89.4%)
Excellent	27 (60.0%)	28 (47.5%)	55 (52.9%)
Good	14 (31.1%)	24 (40.7%)	38 (36.5%)
Moderate	4 (8.9%)	5 (8.5%)	9 (8.7%)
None	0	2 (3.4%)	2 (1.9%)
Based on all injections			
n (b)	50	62	112
Excellent or Good	41 (82.0%)	52 (83.9%)	93 (83.0%)
Excellent	27 (54.0%)	28 (45.2%)	55 (49.1%)
Good	14 (28.0%)	24 (38.7%)	38 (33.9%)
Moderate	4 (8.0%)	5 (8.1%)	9 (8.0%)
None	0	2 (3.2%)	2 (1.8%)
Response not provided	5 (10.0%)	3 (4.8%)	8 (7.1%)

Of the 86 first injections, 81 were evaluated for a response; 75 first injections were rated by subjects as producing an excellent or good response (92.6%).

Number of Injections Required to Resolve a Bleeding Episode:

Overall, 93% of bleeding episodes were controlled with ≤2 injections of Eloctate with 81.4% controlled by 1 injection. The number of bleeding episodes requiring a second injection was 16 bleeding episodes in 11 subjects, with the median time of 23.88 hours elapsed between the first and second dose. The median dose per injection required for resolution of bleeding was 49.69 IU/kg and the median total dose required was 54.90 IU/kg. There were three subjects that required more than 3 injections of Eloctate for resolution of a bleeding episode.

	Age cohort		
Method of Analysis	<6 years old (N=35)	6 to <12 years old (N=34)	Total (N=69)
Per bleeding episode (a)			
1	29 (76.3%)	41 (85.4%)	70 (81.4%)
2	7 (18.4%)	3 (6.3%)	10 (11.6%)
3	1 (2.6%)	2 (4.2%)	3 (3.5%)
4	1 (2.6%)	1 (2.1%)	2 (2.3%)
>4	0	1 (2.1%)	1 (1.2%)
1	29 (76.3%)	41 (85.4%)	70 (81.4%)
>1	9 (23.7%)	7 (14.6%)	16 (18.6%)
<=2	36 (94.7%)	44 (91.7%)	80 (93.0%)
>2	2 (5.3%)	4 (8.3%)	6 (7.0%)
n(b)	38	48	86
Mean	1.3	1.3	1.3
SD	0.66	0.82	0.75
Median	1.0	1.0	1.0
25th, 75th percentile	1.0, 1.0	1.0, 1.0	1.0, 1.0
Min, Max	1, 4	1, 5	1, 5

Additional Efficacy Endpoints included the Physician's global assessment of the subject's response to the Eloctate regimen which was excellent/effective in 99.3% of the subjects' visits.

Reviewer Comment:
This supports the primary efficacy analysis. Eloctate was effective in controlling bleeding for pediatric subjects on routine prophylaxis. Both age cohorts had similar median ABRs. Moreover, most bleeding episodes resolved with one dose and rated excellent/good. Although PK data support a prolonged interval between repeat doses when needed, redosing in children are shorter in comparison to adults given the age-dependent clearance of Eloctate. The results of these data are also comparable to other products.

Surgeries:

No specific objectives were specified for surgeries, but the information on the type of surgery and hemostatic response was collected. There was one major surgery which occurred during the screening period before the subject received his first study dose. There were seven minor surgeries in 7 subjects during the study. Hemostasis were collected at least 24 hours following the procedure and rated as excellent for 5 of the surgeries and good for the remaining 2 surgeries by the surgeon's assessment.

Surgery	Assessment
Tooth Removal	Good
Port-A-Cath Removal	Excellent
Port Placement	Excellent
Implantofix Removal	Excellent
Tooth Removal	Excellent
Colonoscopy	Good
Dental Extraction	Excellent

Reviewer Comment:
Three of the seven minor surgeries were assessed over 48 hours after the surgery (one assessed after 6 months of duration), which is not an accurate assessment of bleeding. Overall, the hemostatic response was excellent or good.

6.1.11.3 Subpopulation Analyses

An analysis that excluded subjects with major protocol deviations including one subject from each age cohort was performed which showed a median ABR of 0.98 and 2.01 for subjects in the <6 years of age cohort and the 6 to<12 years of age cohort, respectively.

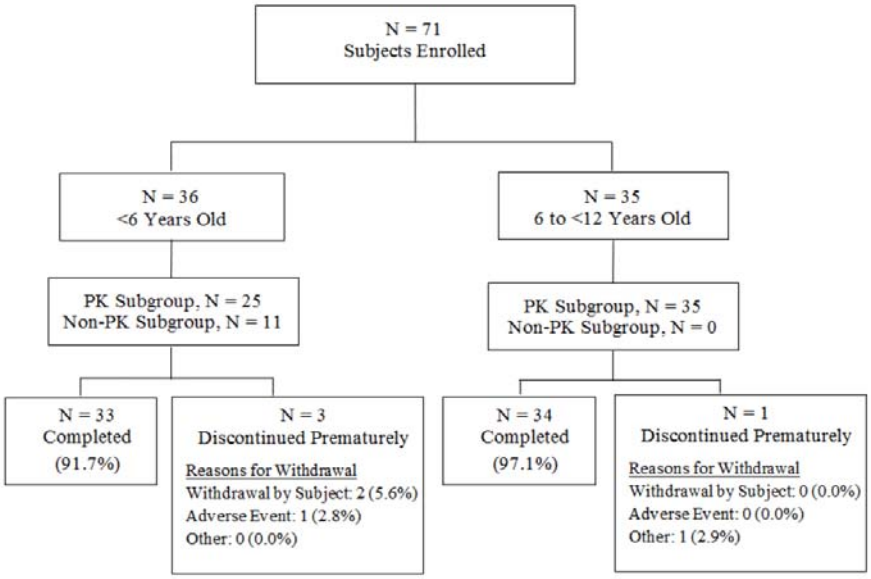
There were 13 subjects with target joints at screening and 56 without target joints at screening. Of those with target joints, six subjects were in the <6 years of age cohort and 7 subjects were in the 6 to <12years of age cohort. The median ABR for those subjects with target joints was 2.03 (25^{h} and 75th percentile: 0.0, 6.0).

Seven subjects were on prior episodic dosing and 62 subjects were on prophylaxis dosing prior to participating in the Efficacy period. The median annualized bleeding rate was 2.05 for subjects on prior episodic dosing and 1.96 for subjects on prior prophylaxis dosing.

Reviewer Comment:
The ABR after exclusion continued to be similar and within the range of accepted ABRs. Those subjects with target joints also showed a similar median ABR rate compared to those without (1.97 vs. 2.03). However, subjects less than 6 years of age without target joints had an ABR of zero, while the 6 subjects <6 years with target joints had an ABR of 2.83, which would be expected in the younger age group with joint disease. Those subjects on episodic dosing had a higher median ABR than those on prophylaxis dosing which is also an expected outcome, as prophylaxis should reduce the annualized bleeding risk and subsequent rate.

6.1.11.4 Dropouts and/or Discontinuations

One subject who was treated with prestudy FVIII experienced an AE (Klebsiella sepsis) that led to discontinuation from the study before administration of Eloctate. Four subjects did not complete the study.



6.1.11.5 Exploratory and Post Hoc Analyses

Please see clinical review memo from the original BLA for complete details.

6.1.12 Safety Analyses

6.1.12.1 Methods

The safety analysis set included 69 subjects who received Eloctate. Among these subjects, 63 were assessed during at least 13 weeks of treatment and 44 subjects during at least 26 weeks of treatment.

6.1.12.2 Overview of Adverse Events

AEs were reported for a total observation period (including follow-up) of 33.1 subject-years for the 69 subjects treated with Eloctate. Of those subjects, 59 subjects (85.5%) reported at least one AE, with a total of 213 AEs. The highest incidence of AEs was infections and infestations. Other system organ class (SOC)s with an AE incidence of ≥10% were respiratory, thoracic and mediastinal disorders (18 subjects; 26.1%); gastrointestinal disorders (16 subjects; 23.2%); musculoskeletal and connective tissue disorders (16 subjects; 23.2%); injury, poisoning, and procedural complications (15 subjects; 21.7%); and general disorders and administration site (9 subjects; 13.0%). Two severe AEs were reported in one subject (streptococcal infection and croup infection).

rFVIIIFc treatment-emergent adverse events by system organ class in descending order of incidence
Safety Analysis Set
Page 1 of 2

System organ class	Age cohort <6 years old (N=36)	6 to <12 years old (N=35)	Total (N=71)
Number of subjects treated with rFVIIIFc	35	34	69
Total number of TEAEs	118	95	213
Number of subjects with at least one TEAE	31 (88.6%)	28 (82.4%)	59 (85.5%)
INFECTIONS AND INFESTATIONS	22 (62.9%)	16 (47.1%)	38 (55.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	10 (28.6%)	8 (23.5%)	18 (26.1%)
GASTROINTESTINAL DISORDERS	9 (25.7%)	7 (20.6%)	16 (23.2%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	7 (20.0%)	9 (26.5%)	16 (23.2%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	8 (22.9%)	7 (20.6%)	15 (21.7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (11.4%)	5 (14.7%)	9 (13.0%)
IMMUNE SYSTEM DISORDERS	3 (8.6%)	3 (8.8%)	6 (8.7%)
NERVOUS SYSTEM DISORDERS	2 (5.7%)	4 (11.8%)	6 (8.7%)
EAR AND LABYRINTH DISORDERS	2 (5.7%)	1 (2.9%)	3 (4.3%)
EYE DISORDERS	1 (2.9%)	1 (2.9%)	2 (2.9%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (5.7%)	0	2 (2.9%)
CARDIAC DISORDERS	1 (2.9%)	0	1 (1.4%)
INVESTIGATIONS	1 (2.9%)	0	1 (1.4%)
METABOLISM AND NUTRITION DISORDERS	1 (2.9%)	0	1 (1.4%)
PSYCHIATRIC DISORDERS	1 (2.9%)	0	1 (1.4%)

Two subjects experienced at least one AE that was assessed as related to Eloctate which included myalgia and erythematous rash. Neither of these events were required a change in study treatment or discontinuation. There were no subjects with a missing assessment of relationship to study treatment. The incidence of AEs was similar between the age cohorts.

6.1.12.3 Deaths

There were no deaths reported in these studies.

6.1.12.4 Nonfatal Serious Adverse Events

Five subjects reported at least one SAE, with a total of 7 SAEs and assessed as not related to Eloctate (2 subjects reported 2 events each).

Summary of rFVIIIFc treatment-emergent serious adverse events
Safety Analysis Set
Page 1 of 2

System organ class Preferred term	Age cohort <6 years old (N=36)	6 to <12 years old (N=35)	Total (N=71)
Number of subjects treated with rFVIIIFc	35	34	69
Total number of TESAEs	5	2	7
Number of subjects with at least one TESAE	4 (11.4%)	1 (2.9%)	5 (7.2%)
INFECTIONS AND INFESTATIONS	2 (5.7%)	1 (2.9%)	3 (4.3%)
BACILLUS INFECTION	0	1 (2.9%)	1 (1.4%)
CROUP INFECTIOUS	1 (2.9%)	0	1 (1.4%)
ESCHERICHIA INFECTION	0	1 (2.9%)	1 (1.4%)
METAPNEUMOVIRUS INFECTION	1 (2.9%)	0	1 (1.4%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (5.7%)	0	2 (2.9%)
FALL	1 (2.9%)	0	1 (1.4%)
HEAD INJURY	2 (5.7%)	0	2 (2.9%)

6.1.12.5 Adverse Events of Special Interest (AESI)

AESI's were specified in the protocol as development of inhibitors, Grade 2 or greater allergic reactions, and thrombotic events.

Development of an inhibitor was defined as an anti-Eloctate neutralizing antibody value ≥0.6 BU/mL confirmed on retesting within 2 to 4 weeks. No inhibitors were reported as SAEs during the study. Of the 71 subjects, 61 had ≥50 EDs to Eloctate. All 61 subjects had an inhibitor test, with an estimated confirmed inhibitor incidence rate of 0% (95% CI: 0, 5.87). No subjects developed inhibitor to FVIII during the study (neither confirmed nor unconfirmed positive inhibitor results were reported).

No SAEs of allergic reactions, anaphylaxis, or serious hypersensitivity events were reported during the study.

No SAEs of vascular thrombotic events were reported.

Three catheter-associated events were reported in 2 subjects during the study: device component issue (possible blocked port) in 1 subject and device occlusion in 1 other subject (blocked port; 2 occurrences). These events were all considered by the Investigator to be mild and unrelated to Eloctate. Two of the 3 events resolved without further treatment; the remaining event was not resolved despite medical treatment. No action was taken with study treatment for any of these events.

No serious bleeding events were treatment-emergent to Eloctate. Non-serious bleeding-related events that were treatment-emergent to Eloctate occurred in 5 subjects; all resolved and were assessed by the Investigator as mild in severity and unrelated to Eloctate.

No subjects in the study were reported to have received an overdose of Eloctate.

6.1.12.6 Clinical Test Results

Clinical laboratory evaluations included hematology (WBC, RBC, and platelet parameters) and blood chemistry (liver function, renal function, electrolyte, and other parameters) as well as ADAs and neutralizing antibodies (inhibitors).
Overall, there were no clinically meaningful trends in actual values or change from baseline in the hematology data. No clinically meaningful changes were observed in the mean actual value or mean change from baseline over time in the blood chemistry parameters in either age cohort or the total.

6.1.12.7 Dropouts and/or Discontinuations

No subject was reported to have discontinued treatment or withdrawn from the study due to AEs. One subject who was treated with a pre-study FVIII product experienced an AE that led to discontinuation from the study before administration of Eloctate.
No subject discontinued study treatment or withdrew from the study due to any other AEs, including inhibitor development or Grade 2 or greater allergic reaction associated with administration of Eloctate.

6.1.13 Study Summary and Conclusions

Eloctate was highly effective in treating bleeding episodes. The median ABR was 0.00 in the <6 years of age and 2.01 in the 6 to <12 years of age cohorts. Overall, 93.0% of

bleeding episodes were controlled with ≤2 injections of Eloctate, with 81.4% of bleeding episodes controlled by 1 injection. Overall, 93 of the 104 evaluable Eloctate injections (89.4%) were rated by subjects as an excellent or good response, 9 (8.7%) were rated as moderate, and 2 (1.9%) were rated as none (no improvement).

The safety profile was assessed in 69 subjects with exposure to Eloctate over a period of 31 weeks. Eloctate was well tolerated. There were no deaths during the study. There were no serious bleeding events reported. There was no inhibitor development. No subject discontinued treatment or withdrew from the study due to Eloctate.

The results from this pediatric study suggest that Eloctate was well tolerated and effective.

6.2 Trial #2 (Study Number: 8HA01EXT）

Extension Study: An Open-Label, Multicenter Evaluation of the Long-Term Safety and Efficacy of Recombinant Human Coagulation Factor VIII Fusion Protein (rFVIIIFc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects With Hemophilia A

6.2.1 Objectives (Primary, Secondary, etc)

The primary objective of the study is to evaluate the long-term safety of Eloctate in subjects with Hemophilia A.

The secondary objective of the study is to evaluate the efficacy of Eloctate in the prevention and treatment of bleeding episodes in subjects with Hemophilia A.

6.2.2 Design Overview

This is an ongoing, open-label, multicenter, long term extension study of IV administration of Eloctate in PTPs with Hemophilia A who have completed the phase 3 study (Study 997HA301), the pediatric study, or any other study with Eloctate.

Enrollment began August of 2011. This study is ongoing and the interim analysis was submitted to provide long-term safety and efficacy data on Eloctate to support marketing authorization applications. This report summarizes data from the ongoing Study 8HA01EXT through the interim data cutoff date of 06 January 2014.
The study period consists of Screening and Treatment. Subjects first dosed with Eloctate when <12 years of age are followed to at least 100 EDs even if Eloctate becomes commercially available.

6.2.3 Population

Subjects met the criteria for entry into a parent study (male subjects with severe Hemophilia, etc.) who were previously treated with a FVIII product (≥50 EDs for subjects <12 years of age and ≥150 EDs for subjects ≥12 years of age), had no measureable inhibitor activity, had platelet count ≥100,000 cells/μL, and were HIV negative or had viral load <400 copies/mL and CD4 count ≥200 cells/mm3. This information was not collected again for entry into this extension study.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Treatment is administered as follows:

Tailored prophylaxis:

- doses of 25 to 65 IU/kg rFVIIIFc every 3 to 5 days or
- dosing 2 times per week at approximately 20 to 65 IU/kg rFVIIIFc on Day 1 and 40 to 65 IU/kg rFVIIIFc on Day 4.

In pediatric subjects from Study 8HA02PED, dose adjustments up to a maximum prophylactic dose of 80 IU/kg and frequency of administration up to every 2 days can be used if necessary to maintain adequate FVIII activity trough levels and prevent spontaneous bleeding events.

Weekly prophylaxis: once weekly dosing of approximately 65 IU/kg.

Personalized prophylaxis: if optimal prophylaxis dosing cannot be achieved using either tailored or weekly prophylaxis, the Investigator may further personalize dosing to meet the needs of individual subjects. The personalized prophylaxis dosing requires consultation with the Sponsor Medical Monitor.

Episodic (on-demand) regimen: the individual dose of Eloctate to treat bleeding episodes is based on the subject's clinical condition and the type and severity of the bleeding event. Subjects <12 years of age entering from Study 8HA02PED do not have the option of an episodic regimen but can receive an episodic regimen once they reach the age of 12 years during the study.

6.2.5 Directions for Use

Please see clinical review memo from the original BLA for complete details.

6.2.6 Sites and Centers

Subjects in this study were enrolled at 72 investigational sites in 22 countries worldwide. The highest enrolling countries were United States (60 subjects), United Kingdom (37 subjects), and South Africa (28 subjects).

6.2.7 Surveillance/Monitoring

Inhibitor testing at each clinic visit (approximately every 6 months) will allow for inhibitor surveillance over the period of 100 EDs for each subject.
The study is to be stopped in the following cases:

- Three subjects develop high titer (i.e., ≥5.00 Bethesda units [BU]/mL) inhibitor.
- An unexpected, serious, or unacceptable risk to the study subjects.

6.2.8 Endpoints and Criteria for Study Success

The primary endpoint is the occurrence of inhibitor development.
The secondary endpoints are as follows:

- The annualized number of bleeding episodes (spontaneous and traumatic) per subject
- The annualized number of spontaneous joint bleeding episodes per subject

- The total number of days of exposure per subject per year
- The consumption of Eloctate as total dose per kg per subject per year
- Physician's global assessment of the subject's response to his treatment regimen using a 4-point scale
- Subject's assessment of response to the treatment of bleeding episodes using a 4-point scale.

Major surgery endpoints are as follows:

- Investigator/Surgeon assessment of hemostatic response to surgery using the 4-point bleeding response scale
- Number of injections and dose per injection to maintain hemostasis during the surgical period.
- Estimated blood loss (mL) during surgery and Postoperative Period
- Number of blood product units transfused during surgery

6.2.9 Statistical Considerations & Statistical Analysis Plan

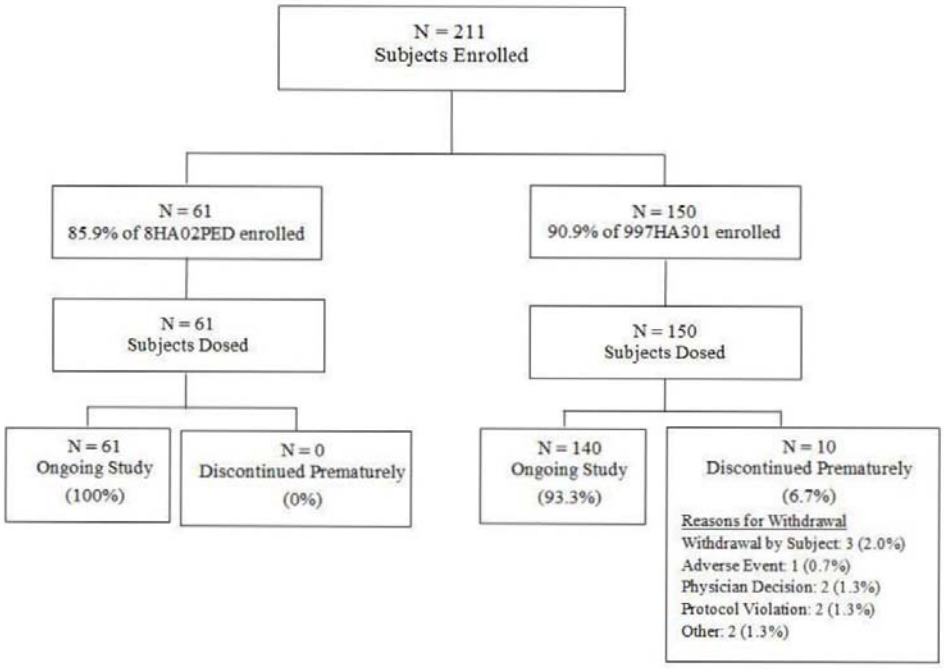
Please see statistical review memo from the original BLA for complete details.

6.2.10 Study Population and Disposition

Enrollment began of August 2011 through the interim data cutoff date of 06 January 2014. This study is ongoing and this interim analysis was to provide long-term safety and efficacy data on Eloctate to support marketing authorization applications.
The study period consists of Screening and Treatment.
Subjects first dosed with Eloctate when <12 years of age are followed to at least 100 EDs even if Eloctate becomes commercially available. All subjects have the opportunity to participate in this study for up to 4 years or until Eloctate is commercially available in the applicable participating country.

6.2.10.1 Populations Enrolled/Analyzed

A total of 211 male subjects, 150 from those ≥12 years (Study 997HA301) and 61 subjects from the pediatric study (Study 8HA02PED ; <12 years) were enrolled in this extension study. There were 15 subjects from the surgery subgroup.
At the time of interim data cutoff, 201 out of 211 remained on study.



6.2.10.1.1 Demographics
All subjects were male and representative of hemophilia A population. The age of subjects ranged from 2 to 66 years at study entry.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Please see clinical review memo from the original BLA for complete details.

6.2.10.1.3 Subject Disposition

The starting dose in the extension study was based on the subjects' results from the preceding Eloctate study. As of the data cutoff of 06 January 2014, the majority of subjects from Study 997HA301 (121 subjects [80.7%]) had completed their 18-month study visit. A total of 22 subjects (36.1%) from Study 8HA02PED had completed their 6-month study visit; 39 subjects had not yet completed their 6-month visit but continued to participate in the study. A total of 10 subjects from Study 997HA301 discontinued the study early.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

No inhibitors were reported.

6.2.11.2 Analyses of Secondary Endpoints

Study 997HA301:
A total of 138 subjects had achieved ≥50 EDs with 70 subjects achieving ≥150 EDs. There were108 subjects on a tailored regimen, 27 subjects on a weekly prophylaxis regimen, and 17 subjects on a personalized prophylaxis regimen, 14 subjects used episodic treatment. 17 subjects switched treatment regimens during the study. The

median dosing interval for subjects who participated in a tailored prophylaxis, weekly prophylaxis, and personalized prophylaxis regimen was 3.51,7.00, and 5.00 days, respectively. The median annualized bleeding rate was 0.66 (IQR: 0.00, 2.63) for subjects on tailored prophylaxis; 2.03 (IQR: 0.60, 4.39) for subjects on weekly prophylaxis; 1.97 (IQR: 0.96, 7.03) for subjects on personalized prophylaxis; and 18.36 (IQR: 10.45, 30.46) for subjects on episodic treatment. Forty-two of 108 subjects (38.9%) on tailored prophylaxis, 6 of 27 subjects (22.2%) on weekly prophylaxis, 4 of 17 subjects (23.5%) on personalized prophylaxis, and 3 of 14 subjects (21.4%) on episodic treatment had no bleeding episodes reported during the Efficacy Period. In these subjects, 77.6%, 80.9%, 87.6%, and 90.8% of first injections with an evaluation for response were rated as excellent or good by the subjects receiving tailored prophylaxis, weekly prophylaxis, personalized prophylaxis, and episodic treatment, respectively. Moreover, 95.0%, 98.6%, 94.3%, and 99.2% of bleeding episodes were controlled with ≤2 injections of Eloctate. Per bleeding episode, the median dose per injection required for resolution of bleeding ranged from 26.88 (episodic) to 46.88 IU/kg (tailored), and the median total dose required ranged from 26.88 (episodic) to 50.00 IU/kg (tailored).

A total of 15 major surgeries were performed in 13 subjects. Hemostasis was rated as excellent or good by the Investigators/Surgeons for 13 major surgeries. A total of 28 minor surgeries were performed in 21 subjects. Hemostasis was rated as excellent or good for these minor surgeries.

Study 8HA02PED:
There were a total of 27 subjects who received ≥50 EDs. A total of 59 of 61 subjects chose a tailored prophylaxis regimen and 2 subjects chose a personalize prophylaxis regimen. No subjects switched treatment regimens. For subjects on a tailored prophylaxis regimen, the median dosing interval was 3.50 days both for subjects in the <6 years of age cohort and for subjects in the 6 to <12 years of age cohort. The median annualized bleeding rate was 0.00 with 25th and 75th percentiles (IQR: 0.00, 2.00) in the <6 years of age cohort and 1.54 (IQR: 0.00, 3.41) in the 6 to <12 years of age cohort. For subjects on tailored prophylaxis, 21 of 29 subjects (72.4%) in the <6 years of age cohort and 14 of 30 subjects (46.7%) in the 6 to <12 years of age cohort had no bleeding episodes reported during the Efficacy Period. In these subjects, 90.5% and 92.6% of first injections with an evaluation were rated as excellent or good by the subjects receiving tailored prophylaxis in the <6 years old cohort and the ≥6 to <12 years old cohort, respectively. Moreover, 95.2% and 89.3% of bleeding episodes were controlled with ≤2 injections of Eloctate. Per bleeding episode, the median dose per injection required for resolution of bleeding was 43.86 and 49.27 IU/kg and the median total dose required was 51.02 and 56.36 IU/kg in the <6 years old cohort and the 6 to <12 years old cohort, respectively.

There were no major surgeries reported for subjects from Study 8HA02PED during the time period for this interim analysis. A total of 3 minor surgeries were performed in 3 subjects. Hemostasis was rated as excellent.

6.2.11.3 Subpopulation Analyses
N/A

6.2.11.4 Dropouts and/or Discontinuations

Of the 10 subjects (4.7%) who discontinued, there were 3 discontinuations due to "withdrawal by subject", 2 due to "physician decision" (non-compliance and non-study FVIII used), 2 due to "protocol violations," 2 due to "other" (1 subject could no longer participate due to incarceration and 1 subject was no longer able to comply with the demands of the study), and 1 due to an AE (elevated serum creatinine).

6.2.11.5 Exploratory and Post Hoc Analyses

N/A

6.2.12 Safety Analyses

6.2.12.1 Methods

Please see clinical review memo from the original BLA for complete details.

6.2.12.2 Overview of Adverse Events

AEs were reported for the 211 subjects treated with Eloctate in the extension study. Of those 211 subjects, 139 subjects (65.9%) reported at least 1 AE, with a total of 427 AEs. Among the 211 subjects treated with Eloctate in the extension study, 3 subjects (1.4%) experienced at least 1 AE that was assessed by the Investigator as related to Eloctate treatment, and 23 subjects (10.9%) reported at least 1 SAE, with a total of 30 SAEs. None of the 23 subjects experienced an SAE that was assessed as related to Eloctate treatment by the Investigator.

6.2.12.3 Deaths

There were no deaths over the course of the study.

6.2.12.4 Nonfatal Serious Adverse Events

Of the 211 subjects treated with Eloctate in the extension study, 23 subjects (10.9%) experienced a total of 29 serious treatment emergent AEs (TEAEs). Of the 29 serious TEAEs reported in 23 subjects, all were assessed by the Investigator as unrelated to Eloctate treatment and none led to discontinuation from the study. None of the serious TEAEs were associated with a fatal outcome; all 29 events had resolved by the time of reporting. Four serious bleeding events were reported as serious TEAEs and one during the perioperative management period for a major surgery. All were assessed as unrelated to Eloctate and all resolved.

6.2.12.5 Adverse Events of Special Interest (AESI)

No SAEs of allergic reaction, anaphylaxis, or serious hypersensitivity reaction associated with Eloctate were reported during the study. Eight subjects experienced nonserious rash or other skin events that could indicate possible allergic reactions. No SAEs of vascular thrombotic events were reported during the study.

6.2.12.6 Clinical Test Results

N/A

6.2.12.7 Dropouts and/or Discontinuations

One subject (0.5%) was reported to have discontinued Eloctate treatment or withdrawn from the study due to an AE.

6.2.13 Study Summary and Conclusions

Overall, the safety profile of Eloctate in the extension study was assessed and showed that Eloctate was well tolerated. These results are similar to the parent studies. The study is currently ongoing.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

N/A

7.1.1 Methods of Integration

N/A

7.1.2 Demographics and Baseline Characteristics

N/A

7.1.3 Subject Disposition

N/A

7.1.4 Analysis of Primary Endpoint(s)

N/A

7.1.5 Analysis of Secondary Endpoint(s)

N/A

7.1.6 Other Endpoints

N/A

7.1.7 Subpopulations

N/A

7.1.8 Persistence of Efficacy

N/A

7.1.9 Product-Product Interactions

N/A

7.1.10 Additional Efficacy Issues/Analyses

N/A

7.1.11 Efficacy Conclusions

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

N/A

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

N/A

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

N/A

8.2.3 Categorization of Adverse Events

N/A

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

N/A

8.4 Safety Results

8.4.1 Deaths

N/A

8.4.2 Nonfatal Serious Adverse Events

N/A

8.4.3 Study Dropouts/Discontinuations

N/A

8.4.4 Common Adverse Events

N/A

8.4.5 Clinical Test Results

N/A

8.4.6 Systemic Adverse Events

N/A

8.4.7 Local Reactogenicity

N/A

8.4.8 Adverse Events of Special Interest

N/A

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

N/A

8.5.2 Time Dependency for Adverse Events

N/A

8.5.3 Product-Demographic Interactions

N/A

8.5.4 Product-Disease Interactions

N/A

8.5.5 Product-Product Interactions

N/A

8.5.6 Human Carcinogenicity

N/A

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

N/A

8.5.8 Immunogenicity (Safety)

N/A

8.5.9 Person-to-Person Transmission, Shedding
N/A

8.6 Safety Conclusions

N/A

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

N/A

9.1.1 Human Reproduction and Pregnancy Data

N/A

9.1.2 Use During Lactation

N/A

9.1.3 Pediatric Use and PREA Considerations

N/A

9.1.4 Immunocompromised Patients

N/A

9.1.5 Geriatric Use

N/A

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

N/A

10. CONCLUSIONS

The objective of the pediatric study was to evaluate the safety and efficacy of Eloctate in previously treated pediatric subjects with severe Hemophilia A. The safety evaluation revealed that Eloctate was well tolerated. No subject developed an inhibitor, had a serious hypersensitivity event, or a vascular thrombotic event. Adverse events were identified without clusters of events identified. For evaluation of efficacy, low annualized bleeding rates were observed in both age cohorts over the course of the study. Eloctate also demonstrated to effectively control bleeding with 81.4% of bleeding episodes resolved with a single injection of Eloctate and nearly all bleeding episodes resolved in 1 or 2 doses. The subject's assessment of response to Eloctate was also rated as excellent or good in the majority of patients. The PK assessment showed a mean clearance that was higher in the younger age cohort than the older cohort. Overall, the completed pediatric study continued to show overall efficacy and safety of Eloctate.

The interim analysis of extension study provided additional data to evaluate the long term safety and efficacy of this product including those from prior studies with sever Hemophilia A. No subject, thus far, had developed an inhibitor. There were no reports of hypersensitivity or vascular thrombotic events, not any clusters of adverse events identified. The additional data from the adult and pediatric subjects continue to show low ABR and are in line with the parent studies.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

See Table below.

Risk Benefit Considerations for Eloctate

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hemophilia A is a hereditary bleeding disorder characterized by recurrent bleeding, which if left untreated bleeds lead to chronic arthropathy, muscular atrophy and deformities. • Treatment of bleeds may delay these complications, but does not prevent it. • Primary prophylaxis with regular FVIII injections initiated at an early age is becoming the standard of care	• Hemophilia A is a hereditary, life-threatening disease • Hemophilia A can have a debilitating impact on physical and psychosocial well-being.
Clinical Benefit	• The final study report for the pediatric trial was submitted along with the ongoing extension study. •The pediatric study of 71 children <12 years and the extension trial with 211 subject, thus far were included. Efficacy was demonstrated for the on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis to reduce the frequency of bleeding episodes. No new safety concerns were identified.	•The evidence for clinical benefit is compelling.
Risk	• The most substantial risks of treatment with ELOCTATE™ are allergic reactions and development of FVIII inhibitors. No confirmed inhibitors or significant allergic reactions were noted during the trial; however, the study may have been underpowered to adequately identify these potential risks. • No serious adverse events were found to be attributable to ELOCTATE™. • No other safety signals were apparent.	• All the evidence indicates that Eloctate was well tolerated.
Risk Management	• The most substantial risks of treatment with ELOCTATE™ are allergic reactions and development of FVIII inhibitors. • No other safety signals were apparent.	• The package insert and the current pharmacovigilance plan, including the post-marketing studies, would be adequate to manage the risks

11.2 Risk-Benefit Summary and Assessment

Benefits:
The efficacy of Eloctate has been established for the on-demand treatment and control of bleeding episodes, perioperative management of bleeding and routine prophylaxis to prevent or reduce the frequency of bleeding episodes, in the pediatric clinical study that enrolled 71 subjects and 211 subjects in the ongoing extension study. The terminal half-life is 1.5 times longer than other licensed FVIII products.

Risks:
The formation of Factor VIII inhibitors was not observed in the pediatric or extension studies. No serious adverse events were found to be attributable to Eloctate.

The risk/benefit profile of Eloctate is favorable.

11.3 Discussion of Regulatory Options

N/A

11.4 Recommendations on Regulatory Actions

This clinical reviewer recommends approval of the labeling changes associated with this efficacy supplement. Efficacy and safety clinical data for Eloctate were found adequate to make a favorable benefit/risk determination and to support approval for the proposed indications of:
• On-demand treatment and control of bleeding episodes,
• Perioperative management of bleeding
• Routine prophylaxis to reduce the frequency of bleeding episodes.

11.5 Labeling Review and Recommendations

The revised package insert (PI) was reviewed, commented, and/or revised by the appropriate discipline reviewers before APLB conducted its review from a promotional and comprehension perspective. Comments and recommendations regarding the PI for this efficacy supplement were initially conveyed to Biogen on 4 November 2015, and negotiated throughout the months of November 2015 to January 2016.

The revised PI includes a statement comparing the terminal half-life of Eloctate to Advate which is supported by the results of the A-LONG Study (997HA301). This statement was accepted in the final PI.

Final version of the PI submitted to the BLA on January 7, 2016 was considered acceptable.

11.6 Recommendations on Postmarketing Actions

N/A

*****Do Not Change Anything Below This Line*****