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Application Type	BLA
STN	125771/136
CBER Received Date	July 13, 2023
PDUFA Goal Date	May 10, 2024
Division / Office	DCEH/OCE/OTP
Committee Chair	Zuben Sauna, Ph.D.
Clinical Reviewer(s)	Megha Kaushal, MD
Project Manager	Niloofar Kennedy
Priority Review	No
Reviewer Name(s)	Jiang Hu, Ph.D.
Review Completion Date / Stamped Date	May 7,2024
Supervisory Concurrence	Lin Huo, Ph.D., Team Lead, TEB2/DB/OBPV
	Lihan Yan, Ph.D., Branch Chief, TEB2/DB/OBPV
Applicant	Bioverativ Therapeutics Inc.
Established Name	efanesoctocog alfa
(Proposed) Trade Name	ALTUVIIIO
Pharmacologic Class	recombinant FVIII
Formulation(s), including Adjuvants, etc	Antihemophilic Factor (Recombinant), Fc-Von Willebrand Factor-XTEN Fusion Protein
Dosage Form(s) and Route(s) of Administration	Lyophilized powder for solution for intravenous injection
Dosing Regimen	50 IU/kg once weekly for routine prophylaxis; 50 IU/kg x 2 (IU/dL per IU/kg) for on-demand treatment and control of bleeding episodes and perioperative management
Indication(s) and Intended Population(s)	For use in adults and children with hemophilia A (congenital factor VIII deficiency) for: (1) Routine prophylaxis to reduce the frequency of bleeding episodes, (2) On-demand treatment & control of bleeding episodes, (3) Perioperative management of bleeding.

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GLOSSARY

ABR	annualized bleeding rate
BLA	Biologics License Application
CI	confidence interval
ED	exposure day
FAS	full analysis set
FVIII	coagulation factor viii
IV	intravenous
PK	pharmacokinetic
PTP	previously treated patients
SAS	safety analysis set
sBLA	supplemental Biologics License Application
SD	standard deviation
TEAE	treatment-emergent adverse event

1. EXECUTIVE SUMMARY

In this supplemental Biologics License Application (sBLA) submission, the Applicant proposed to update the prescribing information for Altuviiio (referred to as BIVV001) to include the efficacy and safety information from the completed pediatric Study EFC16295, in pediatric previously treated patients (PTPs) <12 years of age with severe hemophilia A. This sBLA does not pursue any additional indication for BIVV001.

In Study EFC16295, a total of 74 pediatric subjects with severe hemophilia A were enrolled into 2 cohorts by age (38 in the <6 years of age cohort and 36 in the 6 to <12 years of age cohort). The primary endpoint was the occurrence of inhibitor development to coagulation factor VIII (FVIII), which was not detected during this study. The incidences of inhibitor development in all treated subjects (N=74) and in subjects with ≥50 exposure days (EDs) to FVIII (n=65) were 0.0% (95% confidence interval [CI]: 0.0% to 4.9%) and 0.0% (95% CI: 0.0% to 5.5%), respectively. Two subjects were excluded from the efficacy analyses of annualized bleeding rate (ABR), due to either failure of receiving the specified treatment or lack of duration of exposure to the product. For treated bleeds, the mean ABR estimated from the negative binomial model was 0.61 (95% CI: 0.42 to 0.90) for all subjects (N=72), with 0.48 (95% CI: 0.30 to 0.77) for the <6 years of age cohort and with 0.75 (95% CI: 0.41 to 1.40) for the 6 to <12 years of age cohort. The median (Q1; Q3) ABRs were 0.00 (0.00; 1.00) for all subjects, 0.00 (0.00, 1.05) for the <6 years of age cohort, and 1.00 (0.00, 1.02) for the 6 to <12 years of age cohort. Similarly, for all bleeds including both treated and untreated bleeds, the mean ABR was 2.57 (95% CI: 1.63 to 4.03) for all subjects, with 2.80 (95% CI: 1.39 to 5.63) for the <6 years of age cohort and 2.32 (95% CI: 1.30 to 4.12) for the 6 to <12 years of age cohort. The median (Q1; Q3) ABR was 0.5 (0.0; 2.1) for all subjects, 0.0 (0.0, 2.0) for the <6 years of age cohort and 1.0 (0.0, 2.9) for the 6 to <12 years of age cohort.

For efficacy in control of bleeding, one subject was excluded from analysis due to receiving intensive consolidation treatment of BIVV001. Among 43 bleeding episodes treated during the efficacy period with 73 subjects, 41 bleeding episodes (95.3%) were controlled by a single injection and 2 bleeding episodes required 2 injections for bleed resolution, with both occurring in the <6 years of age cohort. The median (Q1; Q3) total dose to treat a bleeding episode was 52.6 IU/kg (50.0; 55.8).

Two major surgeries were performed in two subjects, both in the <6 years of age cohort. Both subjects subsequently resumed a once-weekly prophylactic BIVV001 dosing of 50 IU/kg during the peri-operative period and both hemostatic responses were rated as excellent.

No death occurred in the study.

Statistical analyses of inhibitor development and ABRs included in the sBLA submission have been verified. No issues have been identified. I recommend approval for the proposed labeling updates.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia A is an X chromosome-linked bleeding disorder. Individuals with severe hemophilia experience frequent bleeding episodes into major joints, soft tissue, and muscle, either spontaneously or following minor trauma. The disease can be acutely life-threatening.

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

Treatments for hemophilia A require replacement with a form of FVIII. All currently marketed FVIII replacement products bind to endogenous von Willebrand factor and are thus subject to a half-life ceiling of approximately 15 to 19 hours. BIVV001 is a von Willebrand factor-independent FVIII replacement therapy, and it provides sustained FVIII activity levels with weekly dosing.

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

BIVV001 was originally approved on February 22, 2023, in the United States and was not approved in any country at the time of the data cut-off for the studies in this submission.

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

BIVV001 was originally submitted under BLA 125771 on June 30, 2022, and approved on February 22, 2023. At that time, the pivotal Phase 3 study in pediatric PTPs (Study EFC16295) was ongoing, and interim efficacy and safety data were submitted for review.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

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

5.1 Review Strategy

The statistical memo reviews the Phase 3 Study EFC16295 and focuses on inhibitor development and ABR analyses.

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

The following documents in BLA 125771/136 were reviewed and served as the basis for this statistical memo:

- 125771/136
  - Module 2.2: Introduction
  - Module 2.5: Clinical overview
  - Module 2.7: Clinical summary
  - Module 5.3.5.2: Clinical study reports, protocols, and statistical analysis plans of Study EFC16295
  - Datasets of individual studies and pooled datasets

BLA 125771/136.1 submitted on January 17, 2024, was also reviewed and included in this memo.

5.3 Table of Studies/Clinical Trials

The clinical overview of the safety and efficacy of BIVV001 in pediatric PTPs <12 years of age with severe hemophilia A (FVIII activity level of <1%) in Study EFC16295 is presented in Table 1.

Table 1. Overview of Study EFC16295

Study Code	Study Description	Number of Subjects	Dosing Regimen and Treatment Duration	Population	Status
EFC16295 Phase 3 Pediatric	Open-label study to assess the safety, efficacy, and PK of BIVV001 in pediatric PTPs with severe hemophilia A, <12 years of age.	74 (38 in <6 years of age cohort; 36 in 6 to <12 years of age cohort)	50 IU/kg once weekly for 52 weeks	Pediatric PTPs with severe hemophilia A (<12 years of age)	Completed

Source: Adapted from BLA 125771/136 Module 2.5: Clinical Overview, Table 1, page 11.
Abbreviations: PK, pharmacokinetics; PTP, previously treated patient.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study EFC16295

6.1.1 Objectives

The primary objective of Study EFC16295 was to evaluate the safety of BIVV001 in previously treated pediatric subjects with hemophilia A.

Secondary objectives included:

- To evaluate the efficacy of BIVV001 as a prophylaxis treatment
- To evaluate the efficacy of BIVV001 in the treatment of bleeding episodes
- To evaluate BIVV001 consumption for the prevention and treatment of bleeding episodes
- To evaluate the effect of BIVV001 prophylaxis on joint health outcomes

- To evaluate the effect of BIVV001 prophylaxis on QoL quality of life outcomes
- To evaluate the efficacy of BIVV001 for perioperative management
- To evaluate the safety and tolerability of BIVV001 treatment
- To assess the PK of BIVV001 based on the one-stage activated partial thromboplastin time and (b) (4) chromogenic FVIII activity assays

6.1.2 Design Overview

This was a multinational, multicenter, open-label Phase 3 study to evaluate the safety, efficacy, and PK of BIVV001 in PTPs <12 years of age with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII).

The study was composed of two age cohorts (<6 years of age and 6 to <12 years of age), and subjects received intravenous (IV) BIVV001 at a dose of 50 IU/kg once weekly for 52 weeks. Originally, 65 subjects were planned to be enrolled to achieve at least 50 subjects (25 subjects <6 years of age and 25 subjects 6 to <12 years of age) completing approximately 52 weeks of treatment with at least 50 EDs, and at least 12 subjects in each age cohort needed to have completed adequate blood sample collection to assess key PK parameters. The planned number was increased from 65 to 75 to achieve sufficient fully evaluable PK profiles based on the study protocol and pediatric investigation plan requirements of subjects in the <6 years of age cohort.

6.1.3 Population

Subjects enrolled in this study were PTPs with severe hemophilia A aged younger than 12 years of age. Previous treatment of hemophilia A (prophylaxis or on-demand) was defined as any recombinant and/or plasma-derived FVIII, or cryoprecipitate for at least 150 EDs in patients aged 6 to 11 years or at least 50 EDs for patients aged <6 years of age. Subjects with a history of a positive inhibitor test or with a positive inhibitor result at screening were excluded.

6.1.4 Study Treatments or Agents Mandated by the Protocol

For prophylaxis, subjects received a weekly dose of 50 IU/kg IV.

For on demand treatment, a single dose of 50 IU/kg IV was applied for all bleeding episodes. If a bleeding episode does not improve, additional doses of 30 or 50 IU/kg every 2 to 3 days might be considered. For minor/moderate bleeding episodes occurring within 2 to 3 days after a recent prophylactic dose, an initial 30 IU/kg dose might also be used.

For perioperative management, a single dose of 50 IU/kg IV was administered for all subjects. Additional doses of 30 or 50 IU/kg every 2 to 3 days might be administered for major surgery.

6.1.6 Sites and Centers

Subjects were screened at 39 study centers and enrolled from 37 study centers in 15 different countries (USA, Canada, France, Germany, Hungary, Ireland, Italy, Netherlands, Spain, Sweden, Switzerland, UK, Turkey, Australia, and Taiwan).

6.1.7 Surveillance/Monitoring

Study centers were monitored by the Applicant in all countries. Centers were visited at regular intervals and a Visit Log was maintained. Monitors were responsible for reviewing adherence to the protocol; compliance with Good Clinical Practice; and the completeness, accuracy, and consistency of the data.

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint for this study was the occurrence of inhibitor development, defined as an inhibitor result of ≥0.6 BU/mL. The primary analysis of inhibitor development is based on all subjects who have reached at least 50 EDs and had at least 1 inhibitor test performed at or beyond this milestone.

Selected secondary endpoints of Study EFC16295 included ABRs, hemostatic efficacy for controlling bleeding, and hemostatic response during surgeries.

Sample Size Determination

The determination of the number of subjects was based on clinical rather than statistical considerations.

Analysis Populations

The all-enrolled analysis set included all subjects who were enrolled in the study, regardless of whether they were dosed with study drug or not.

The full analysis set (FAS) included all subjects who received at least one dose of study drug. All analyses of demographics, baseline characteristics, and efficacy were based on the FAS.

The per-protocol set was a subset of the FAS including subjects who did not have important protocol deviations potentially impacting efficacy. The per-protocol set was utilized for analysis of the key secondary efficacy endpoint, as well as sensitivity analysis of the primary endpoint.

The safety analysis set (SAS) was the same as the full analysis set and included all subjects who receive at least one dose of study drug. All analyses of safety were based on the SAS, unless otherwise specified.

Statistical Analyses

For the primary endpoint, the overall incidence of positive inhibitor formation was calculated as: (Number of subjects with an inhibitor) / (Number of subjects reaching 50 EDs or who have an inhibitor). The incidence was summarized for each age cohort and overall, with associated exact 95% CIs using the Clopper-Pearson method.

The secondary endpoint of ABR was analyzed using the FAS including subjects with an efficacy period of at least 26 weeks. The mean and 95% CI of ABR was estimated using a negative binomial model. The model included the number of treated bleeding episodes during the efficacy period as response variable, log-transformed duration of efficacy period as offset variable to account for variable duration.

All secondary efficacy endpoints were summarized descriptively based on the FAS and presented by age cohort and overall, unless otherwise specified. All analyses of bleeding endpoints were reported based on treated bleeding episodes, except for the summary of ABR for all bleeds which include both treated and untreated bleeds.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

In total, 79 subjects were screened for the study; 5 (6.3%) were screen failures: 3 (3.8%) met exclusion criteria and 2 (2.5%) did not meet the inclusion criteria.

Table 2. Analysis Populations, Study EFC16295

Study Population	<6 Years of Age Cohort	6 to <12 Years of Age Cohort	Overall
Full analysis set	38	36	74
Safety analysis set	38	36	74
Per-protocol set	38	36	74
PK analysis set	19	18	37
Surgery subgroup	2	0	2

Source: Adapted from BLA 125771/136 Module 5.3.5.2: CSR for Study EFC 16925, Table 6, page 26.
Abbreviations: PK, pharmacokinetics.

6.1.10.1.1 Demographics

At the data cut-off date, all 74 pediatric subjects in the FAS were male.

As shown in Table 3, the mean (standard deviation [SD]) age of all subjects was 5.99 (2.91) years. In the <6 years of age cohort, the mean (SD) age was 3.69 (1.21) years (range: 1.4 to 5.0 years), and in the 6 to <12 years of age cohort, the mean (SD) was 8.42 (2.08) years (range: 6.0 to 11.0 years).

The mean (SD) weight was 17.93 (3.53) kg (range: 11.4 to 25.7 kg) for subjects <6 years of age and 35.79 (12.86) kg (range: 17.2 to 66.5 kg) for subjects aged 6 to <12 years of age.

Three geographic regions were represented in the study: North America (28 subjects [37.8%]), Europe (27 subjects [36.5%]), and Asia/Pacific (19 subjects [25.7%]).

Table 3. Summary of Demographic and Baseline Characteristics, Full Analysis Set

Demographics/ Characteristics	<6 Years of Age Cohort n=38	6 to <12 Years of Age Cohort n=36	Surgery Subgroup n=2	Overall N=74
Age (year)				
Mean (SD)	3.69 (1.21)	8.42 (2.08)	2	5.99 (2.91)
Median	4.0	8.0	4.50	5.0
Min; max	1.4; 5.0	6.0; 11.0	4.0; 5.0	1.4; 11.0
Sex				
Male	38	36	2	74
Female	0	0	0	0
Ethnicity				
Hispanic or Latino	2 (5.3)	1 (2.8)	0	3 (4.1)
Not Hispanic	36 (94.7)	33 (91.7)	2	69 (93.2)
Not reported	0	2 (5.6)	0	2 (2.7)
Race				
Asian	4 (10.5)	4 (11.1)	0	8 (10.8)
Black of African American	1 (2.6)	2 (5.6)	0	3 (4.1)
White	30 (78.9)	25 (69.4)	2	55 (74.3)
Not reported	0	4 (11.1)	0	4 (5.4)
Other	3 (7.9)	1 (2.8)	0	4 (5.4)
Region				
Asia/Pacific	11 (28.9)	8 (22.2)	1	19 (25.7)
Europe	7 (18.4)	20 (55.6)	0	27 (36.5)
North America	20 (52.6)	8 (22.2)	1	28 (37.8)
Weight (kg)				
Mean (SD)	17.93 (3.53)	35.79 (12.86)	19.80 (0.14)	26.62 (12.90)
Median	18.00	32.85	19.80	22.05
Min; max	11.4; 25.7	17.2; 66.5	19.7; 19.9	11.4; 66.5

Source: Adapted from BLA 125771/0 Module 5.3.5.1: CSR for Study EFC 16925, Table 8, page 29.
Abbreviations: SD, standard deviation.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

At study entry, 71 of the 74 enrolled subjects (95.9%) had a documented FVIII activity level below 1% and 3 subjects had a documented genotype known to produce severe hemophilia A. The mean (SD) age at diagnosis was 0.50 (0.80) years, ranging from birth to 4 years.

The distribution of genotypes was representative of a population with severe hemophilia A. More than half of subjects had genotypes associated with inhibitor development to FVIII. Most of the subjects (55 out of 74) had no family history of an inhibitor. No subject was HIV, HBV, or HCV positive.

Overall, the mean (SD) age at start of first prophylactic treatment was 1.0 (1.0) year (range 0 to 5): 60 subjects (81.1%) had prior exposure to recombinant FVIII and 14 subjects (18.9%) to plasma derived FVIII. At time of screening, the FVIII products most frequently used were: efmoroctocog alfa (38 subjects [51.4%]) and rurioctocog alfa pegol (12 subjects [16.2%]). Per protocol, this previously treated population had ≥50 EDs in the <6 years of age cohort and ≥150 ED in the 6 to <12 years of age cohort.

6.1.10.1.3 Subject Disposition

The SAS and FAS were composed of 74 subjects (100%) who received at least 1 injection of BIVV001. The FAS with an efficacy period included 74 subjects (100%) who received at least 2 prophylactic injections.

A total of 37 subjects were included in the PK subgroup and were evaluable, including 19 in the <6 years of age cohort and 18 in the 6 to <12 years of age cohort.

Two subjects had undergone two major surgeries and eight subjects had undergone nine minor surgeries during the study.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary endpoint of this study is the occurrence of inhibitor development. Please refer to Section 6.1.12.

6.1.11.2 Analyses of Secondary Endpoints

Overview of Annualized Bleeding Rate

Among the 74 subjects in FAS, two subjects were excluded from the primary analysis: one didn't receive the weekly prophylaxis treatment as specified and the other had <26 weeks of exposure i.e., 3 EDs/1.1 weeks of duration. The final efficacy analysis results with 72 subjects were summarized in Table 4. The mean ABR estimated from the negative binomial model for all treated bleeds was 0.61 (95% CI: 0.42 to 0.90), with 0.48 (95% CI: 0.30 to 0.77) for the <6 years of age cohort and 0.75 (95% CI: 0.41 to 1.40) for the 6 to <12 years of age cohort. The median (Q1; Q3) ABR was 0.0 (0.0; 1.0) for all subjects, 0.0 (0.0, 1.0) for the <6 years of age cohort and 1.0 (0.0, 1.1) for the 6 to <12 years of age cohort. Similarly, the mean ABR for all bleeds estimated was 2.57 (95% CI: 1.63 to 4.03), with 2.80 (95% CI: 1.39 to 5.63) for the <6 years of age cohort and 2.32 (95% CI: 1.30 to 4.13) for the 6 to <12 years of age cohort. The median (Q1; Q3) ABR was 0.0 (0.0; 2.1) for all subjects, 0.0 (0.0, 2.0) for the <6 years of age cohort and 1.0 (0.0, 2.9) for the 6 to <12 years of age cohort.

Table 4. Annualized Bleeding Rate

Bleeding Episodes	<6 Years of Age Cohort N=37	6 to <12 Years of Age Cohort N=35	Overall N=72
Treated bleeds			
Mean ABR (95% CI)	0.48 (0.30; 0.77)	0.75 (0.41;1.40)	0.61 (0.42; 0.90)
Median ABR (Q1; Q3)	0.00 (0.00; 1.00)	0.00 (0.00; 1.05)	0.00 (0.00; 1.02)
Number (%) of subjects with ABR=0	23 (62.2)	23 (65.7)	46 (63.9)
Spontaneous bleeds			
Mean ABR (95% CI)	0.17 (0.08; 0.38)	0.15 (0.04;0.55)	0.16 (0.08; 0.31)
Median ABR (Q1; Q3)	0.00 (0.00; 1.00)	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)
Number (%) of subjects with ABR=0	31 (83.8)	32 (91.4)	63 (87.5)
Joint bleeds			
Mean ABR (95% CI)	0.20 (0.06; 0.62)	0.41 (0.19;0.89)	0.30 (0.16; 0.57)
Median ABR (Q1; Q3)	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)
Number (%) of subjects with ABR=0	33 (89.2)	27 (77.1)	60 (83.3)
All bleeds (treated and untreated)			
Mean ABR (95% CI)	2.80 (1.39; 5.63)	2.32 (1.30; 4.13)	2.57 (1.63; 4.03)
Median ABR (Q1; Q3)	0.00 (0.00; 1.97)	1.00 (0.00; 2.89)	0.00 (0.00; 2.04)
Number (%) of subjects with ABR=0	20 (54.1)	16 (45.7)	36 (50.0)

Source: Adapted from BLA 125771/136.1: Response to FDA Clinical Information Request.pdf, Table 1, page 5.
Abbreviations: ABR, annualized bleeding rate.

Number of Injections and Dose of BIVV001 to Treat a Bleeding Episode

Among 43 treated bleeding episodes during the efficacy period within 73 subjects, 41 bleeding episodes (95.3%) were controlled by a single injection and 2 bleeding episodes required 2 injections for bleed resolution, both occurring in the <6 years of age cohort. The median (Q1; Q3) total dose to treat a bleeding episode was 52.6 IU/kg (50.0; 55.8).

One subject was excluded from the FAS for the above analysis because this subject received an intensive consolidation treatment regimen of BIVV001 for an extended period following the treatment of two traumatic hip bleeds. Overall, this subject experienced a total of 21 reported and derived bleeding episodes of which 11 required 1 injection, 8 required 2 injections, and 2 required 4 injections for bleed resolution.

Perioperative (Surgical) Management

Two major surgeries were performed in two subjects, both in the <6 years of age cohort. These involved dental restoration including one tooth extraction in one and circumcision in the other. The dosing of BIVV001 in the surgical treatment period was initiated with one single preoperative (loading) doses of 61.9 IU/kg and 60.4 IU/kg, respectively. A second dose of 37.1 IU/kg was administered in the subject who underwent dental surgery two days after the surgery. Both subjects subsequently resumed a once-weekly prophylactic BIVV001 dose of 50 IU/kg during the perioperative period. The hemostatic response to BIVV001 was rated as excellent for both subjects.

Combined with the result from Study EFC16293 (NCT04161495), a study in adults and adolescents reviewed in the original BLA submission, perioperative hemostasis was

assessed in 14 major surgeries in 13 subjects (10 adults, 3 children). Of the 14 major surgeries, 13 surgeries required a single preoperative dose to maintain hemostasis during surgery. The hemostatic response of BIVV001 was rated as “excellent” in 14 of 14 surgeries (100%).

Nine minor surgeries were performed in eight subjects in this study. Combined with the result from Study EFC16293, the hemostasis was assessed in 27 minor surgeries in 23 subjects (12 adults and 11 adolescents and children). The hemostatic response was evaluated in 21 of these minor surgeries and an “excellent” response was reported in all.

Remark: There were 14 major surgeries in 13 subjects and 19 minor surgeries in 15 subjects reported in Study EFC16293. However, two major surgeries and one minor surgery were undertaken after the last dose of BIVV001; therefore, these surgeries were excluded for the labeling.

6.1.11.3 Subpopulation Analyses

Subgroup analyses were not performed because no inhibitor development was observed in this study.

6.1.12 Safety Analyses

6.1.12.1 Analyses of Primary Endpoint

The primary endpoint of this study was the occurrence of inhibitor development to FVIII (neutralizing antibodies), defined as an inhibitor result of ≥0.6 BU/mL that was confirmed by a second test result from a separate sample, drawn 2 to 4 weeks following the date when the original sample was drawn. No inhibitor development was detected in this study. In all treated subjects (N=74) and in subjects with ≥50 EDs to BIVV001 (N=65), the incidences of inhibitor development to FVIII were 0.0% (95% CI: 0.0 to 4.9) and 0.0% (95% CI: 0.0 to 5.5), respectively.

6.1.12.3 Deaths

No deaths were reported during the study.

6.1.12.4 Nonfatal Serious Adverse Events

Of the 74 subjects in the SAS, 62 (83.8%) experienced a total of 255 treatment-emergent adverse events (TEAEs): 33 subjects (86.8%) in the <6 years of age cohort experienced 146 TEAEs, 29 subjects (80.6%) in the 6 to <12 years of age cohort experienced 108 TEAEs, and 1 TEAE was reported in the surgery subgroup. Overall, 10 treatment-emergent serious adverse events were reported in 9 subjects (12.2%), including 5 subjects <6 years of age and 4 subjects 6 to <12 years of age. No TEAEs resulting in death or leading to treatment discontinuation were reported.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

This memo reviews the completed Phase 3 pediatric Study EFC16295.

In Study EFC16295, 74 pediatric PTPs with severe hemophilia A were enrolled into 2 cohorts by age (<6 years of age and 6 to <12 years). This study included 38 subjects <6 years of age and 36 subjects 6 to <12 years of age. The primary endpoint was the occurrence of inhibitor development to FVIII. No FVIII inhibitors were detected in all treated subjects during the one-year study. The incidences of inhibitor development to FVIII were 0.0% (95% CI: 0.0 to 4.9) for all treated subjects (N=74) and 0.0% (95% CI: 0.0 to 5.5) for subjects with ≥50 EDs to BIVV001 (n=65) during the one-year study. The mean ABR estimated from the negative binomial model was 0.61 (95% CI: 0.42 to 0.90) for all subjects (N=72), with 0.48 (95% CI: 0.30 to 0.77) for the <6 years of age cohort and 0.75 (95% CI: 0.41 to 1.40) for the 6 to <12 years of age cohort. The median (Q1; Q3) ABRs were 0.00 (0.00; 1.00) for all subjects, 0.00 (0.00, 1.05) for the <6 years of age cohort, and 1.00 (0.00, 1.02) for the 6 to <12 years of age cohort. Similarly, for all bleeds including both treated and untreated, the mean ABR was 2.57 (95% CI: 1.63 to 4.03) for all subjects, with 2.80 (95% CI: 1.39 to 5.63) for the <6 years of age cohort and 2.32 (95% CI: 1.30 to 4.12) for the 6 to <12 years of age cohort. The median (Q1; Q3) ABR was 0.5 (0.0; 2.1) for all subjects, 0.0 (0.0, 2.0) for the <6 years of age cohort, and 1.0 (0.0, 2.9) for the 6 to <12 years of age cohort.

Among 43 bleeding episodes that were treated during the efficacy period within 73 subjects, 41 bleeding episodes (95.3%) were controlled by a single injection and only 2 bleeding episodes required 2 injections for bleed resolution, both occurring in the <6 years of age cohort. The median (Q1; Q3) total dose to treat a bleeding episode was 52.6 IU/kg (50.0; 55.8).

Two major surgeries were performed in two subjects, both in the <6 years of age cohort. Both subjects subsequently resumed a once-weekly prophylactic BIVV001 dose of 50 IU/kg during the perioperative period and both hemostatic responses were rated as excellent.

No deaths occurred in Study EFC16295.

10.2 Conclusions and Recommendations

The statistical analyses of inhibitor development and ABRs included in the sBLA submission have been verified. No issues have been identified. I recommend approval for the proposed labeling updates.