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BLA Clinical Review Memorandum

Application Type	Efficacy Supplement
STN	125771/136
CBER Received Date	July 13, 2023
PDUFA Goal Date	May 10, 2024
Division / Office	OCE/DCEH
Priority Review (Yes/No)	No
Reviewer Name(s)	Megha Kaushal, Branch Chief (Acting), Benign Hematology
Review Completion Date / Stamped Date	5/7/2024
Supervisory Concurrence	'Lola Fashoyin-Aje, Director OCE
Applicant	Bioverativ Therapeutics Inc
Established Name	Efanesoctocog Alfa
(Proposed) Trade Name	Altuviiio
Pharmacologic Class	Recombinant human factor VIII-Fc-VWF-XTEN
Formulation(s), including Adjuvants, etc.	Intravenous Injection
Dosage Form(s) and Route(s) of Administration	Lyophilized Powder for Injectable Solution
Dosing Regimen	For Routine Prophylaxis: 50IU/kg once weekly; For On-Demand treatment and control of bleeding episodes and Perioperative management: 50IU/kg
Indication(s) and Intended Population(s)	For use in adults and children with Hemophilia A for: Routine prophylaxis to reduce the frequency of bleeding episodes; On-Demand treatment and control of bleeding episodes; Perioperative management of bleeding.
Orphan Designated (Yes/No)	Yes

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GLOSSARY

ABR	annualized bleeding rate
ADA	antidrug antibody
AE	adverse event
BLA	Biologics License Application
BU	Bethesda unit
CI	confidence interval
CMC	chemistry, manufacturing, and controls
ED	exposure day
FDA	U.S Food and Drug Administration
FVIII	coagulation factor VIII
HA	Hemophilia A
IND	Investigational New Drug
IU	International units
IV	intravenous
PK	pharmacokinetic
PREA	Pediatric Research Equity Act
PTP	previously treated patient
rFVIII	recombinant FVIII
SAE	serious adverse event
SD	standard deviation
VWF	von Willebrand Factor

1. EXECUTIVE SUMMARY

On July 13, 2023, Bioverativ Therapeutics submitted a BLA supplement to 125771 for Altuviiio to include the completed pediatric study results.

Altuviiio is a recombinant coagulation factor VIII Fc-von Willebrand factor-XTEN fusion protein (rFVIIIFc-VWF-XTEN, Efanesoctocog alfa) product, with a pharmacokinetic (PK) profile independent of VWF. It will be referred to as BIVV001.

BIVV001 was approved on February 22, 2023. Clinical trials that provided evidence for safety and efficacy of BIVV001 were conducted under Investigational New Drug (IND) application 17464. Two primary studies in previously treated adult and pediatric subjects supported the marketing approval of BIVV001 for the following target indications for use in adults and children with Hemophilia A (HA):

- Routine prophylaxis treatment to reduce the frequency of bleeding episodes
- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding

At the time of approval, the pivotal Phase 3 study in previously treated pediatric patients (EFC16295; NCT04759131) was ongoing, and interim efficacy and safety data were submitted for review. This submission of the supplemental Biologics License Application (sBLA) provides the final clinical study report for the Study EFC16295 and the pooled surgery and safety data from the Phase 3 study. Since BIVV001 is currently approved for pediatric subjects, this submission provides updated efficacy and safety data for the pediatric study which are incorporated in the label.

The completed Study EFC16295 was the primary study evaluated under this sBLA submission. Study EFC16295 is a multicenter, open-label study to evaluate the PK, safety, and efficacy of treatment with BIVV001 for prophylaxis and treatment of bleeds in previously treated pediatric subjects (<12 years of age) with severe HA. The safety and efficacy of BIVV001 were evaluated in a total of 74 previously treated subjects in the pediatric study who received at least one dose of BIVV001.This evaluation included an additional 51 subjects to the analysis, as the interim analysis only included subjects with an efficacy period of at least 26 weeks (n=23).

There were 74 subjects <12 years of age treated with BIVV001. Seventy three were treated for an efficacy period of greater than 26 weeks. Seventy-two subjects were efficacy evaluable and had a mean annualized bleeding rate (ABR) (95% CI) of 2.6 (1.6, 4.0) and median of ABR of 0.5 (0, 2.1) for all bleeds. The mean treated ABR was 0.6 (95% CI: 0.4, 0.9) and median of ABR (Q1, Q3) of 0 (0, 1.0) compared to a pre-BIVV001 administration baseline mean treated ABR (standard deviation; SD) of 2.1 (4.2) and median of 1.0 (0; 32). The most common AEs were upper respiratory tract infections and pyrexia which were mild and transient. There were no inhibitors detected. No new safety signals were noted in the pediatric population.

Perioperative management was evaluated for two subjects who required two major surgical procedures and were treated with BIVV001 for surgical hemostasis. Treatment with BIVV001 provided good or excellent hemostatic control in both major surgeries.

This submission did not trigger Pediatric Research Equity Act (PREA) due to Orphan Drug Designation. There are no postmarketing commitments or requirements.

Conclusion and Recommendation

Based on the review of the submitted data, this application has provided the completed pediatric study with substantial evidence of the safety and effectiveness of BIVV001 in children with HA based on an adequate and well-controlled study. Approval to support use in the perioperative setting for pediatric patients was based on an analysis of PK comparability. The completed study continues to support the safe and effective use of BIVV001 in pediatric patients. The overall benefit-risk profile of BIVV001 remains favorable for approved use in adults and children with HA for routine prophylaxis to reduce the frequency of bleeding episodes; on-demand treatment and control of bleeding episodes; and perioperative management of bleeding.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Demographics and baseline characteristics are summarized in Table 1.

Table 1. Demographics and Baseline Characteristics, Study EFC16295

Patient Age	<6 Years	6 to <12 Years	Overall
N	38	36	74
Male, n (%)	38 (100)	36 (100)	74 (100)
Race, n (%)			
Not reported	0	4 (11.1)	4 (5.4)
White	30 (78.9)	25 (69.4)	55 (74.3)
Black	1 (2.6)	2 (5.6)	3 (4.1)
Asian	4 (10.5)	4 (11.1)	8 (10.8)
Other	3 (7.9)	1 (2.8)	4 (5.4)
Ethnicity, n (%)			
Hispanic/Latino	2 (5.3)	1 (2.8)	3 (4.1)
Age			
Mean (SD)	3.7 (1.2)	8.4 (2.1)	6 (2.9)
Median (min, max)	4 (1.4,5)	8 (6, 11)	5 (1.4,11)

Source: Adapted from BLA 125771/136 Clinical Study Report Table 8 page 29
Abbreviations: max, maximum; min, minimum; SD, standard deviation.

Reviewer Comment: *Black and Hispanic subjects are underrepresented populations in this study, relative to the population with the disease (the general population in the US for Hemophilia are comprised of ~12% for Blacks and ~16% for Hispanics). The White population seems adequately represented. The mean and median age are lower as this reflects the study being conducted in pediatric patients.*

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	6.1.11.5
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	

☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

HA is an X-linked congenital bleeding disorder caused by a deficiency of functional FVIII which manifests as bleeding episodes. 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. A study of 21,748 male patients receiving care in federally supported specialized hemophilia treatment centers indicates that the majority (76.5%) had hemophilia A (Soucie et al. 2020). The mean and median age of the cohort was 23.5 and 19 years, respectively. Compared to the distribution of individuals in the general US population, patients with hemophilia in this study who were White comprised 81% of study population versus 72.4% of US general population. Blacks or African Americans comprised 11.2% in the study cohort versus 12.6% in the general population, while for Asians those rates were 3.6% versus 4.8%. The proportion of those with Hispanic ethnicity (16%) was the same as in the general population (16.3%).

The relationship of bleeding severity correlates with clotting factor level. Patients with <0.01 IU/mL or <1% functional FVIII are categorized as having severe HA with spontaneous bleeding into joints or muscles. Moderate and mild cases of HA are characterized by clotting factor levels of 1% to 5% and 5% to <40%, respectively.

The severity of bleeding manifestations in hemophilia generally correlates with the degree of the clotting factor deficiency and can be acutely life threatening. Joint bleeding is the most frequent bleeding manifestation in children and adults. Repeated bleeding into the joints is debilitating and causes development of target joints from inflammation

due to prior bleeding. To prevent joint destruction, the standard of care in patients 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 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 (rFVIII) 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.

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

Currently, there are over 10 licensed rFVIII products, some of which are full-length FVIII products and others that are beta domain deleted products. These products are indicated for adults and children with HA for the control and prevention of bleeding episodes, and/or perioperative management, and/or routine prophylaxis to reduce the frequency of bleeding episodes and the risk of joint damage. The currently approved FVIII products are summarized in Table 2.

Table 2. Approved FVIII Biologics

Product	Category	Full Length or Beta Domain Deleted	Cell Expression	Year Approved
Recombinate	Recombinant	FL	CHO	1992
Kogenate	Recombinant	FL	BHK	1993
Refacto	Recombinant	BDD	CHO	2000
Advate	Recombinant, Plasma/Albumin Free	FL	CHO	2003
Xyntha	Recombinant	BDD	CHO	2008
Novoeight	Recombinant	BDD	CHO	2013
Eloctate	Recombinant, Fc Fusion Protein	BDD	HEK	2014
Obizur	Recombinant, Porcine Sequence	BDD	BHK	2014
Nuwiq	Recombinant	BDD	HEK	2015
Adynovate	Recombinant, 20kDA PEGylated	FL	CHO	2015
Afstyla	Recombinant, Single Chain	BDD	CHO	2016
Kovaltry	Recombinant	FL	BHK	2016
Jivi	Recombinant, 60kDA PEGylated	BDD	BHK	2018
Esperoct	Recombinant, 40kDA PEGylated	BDD	CHO	2019
Altuviiio	Recombinant, Fc-vWF-XTEN fusion	BDD	HEK	2023

Source: FDA review
Abbreviations: BDD, beta domain deleted; BHK, baby hamster kidney; CHO, Chinese hamster ovary; FL, full length; FVIII, coagulation factor VIII; HEK, human embryonic kidney.

2.3 Safety and Efficacy of Pharmacologically Related Products

Inhibitor formation and pathogen transmission are the main safety concerns when using FVIII replacement therapy to treat patients with HA. FVIII concentrates derived from human plasma first became available in the 1960s. The high risk of viral transmission from human plasma donors, underscored by the HIV epidemic in the 1980s, led to the development of rFVIII products that became available in the 1990s. The rFVIII products are genetically engineered and manufactured from animal cell lines, thus minimizing the risk of transmitting human pathogens. Full-length and modified rFVIII have been produced in Chinese hamster ovary or baby hamster kidney cells. In addition to the risk of pathogen transmission, the development of neutralizing antibodies, or inhibitors, has been and remains the most concerning safety issue following the administration of FVIII concentrates. The etiology of the development of inhibitors is thought to be a host immune response triggered by nonhuman proteins contained in the final rFVIII product. Purification steps in the manufacturing processes of successive generations of rFVIII aim to reduce both the transmission of pathogens and the development of inhibitors, which occurs in up to 30% of patients with severe HA (Gouw et al. 2013).[4]

The development of inhibitors decreases the efficacy of replacement therapy, necessitates FVIII dosage increases and/or the use of "bypass" agents, increases the risk of unmanageable bleeding, and increases cost of treatment (by 3-5-fold) (Calvez et al. 2014).[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 incidence from 3%-52%) (Collins et al. 2014; Vezina et al. 2014; Fischer et al. 2015). Incidence of inhibitor development in previously treated patients (PTPs) who have not previously developed an FVIII inhibitor is lower, reported as 0.9% to 4%. Potential risk factors for inhibitor development include genetic factors such as the type of FVIII gene mutation, human leukocyte antigen type, polymorphisms in immune regulatory regions, family history of inhibitors, and ethnic background; 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 subjects were exposed to BIVV001 for the first time under IND 17464 and the original BLA 125771/0.

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

The FDA had multiple interactions with the Applicant throughout the pre-IND, IND, and BLA processes. Key meetings and correspondence are detailed below:

- An End-of-Phase 2 meeting was conducted in 2019.
- In 2021, FDA granted Fast Track Designation. Clinical Outcome Assessment feedback was communicated in July of 2021.
- In April of 2022, a pre-BLA meeting was conducted where FDA agreed on a rolling submission to include interim analysis data for the pediatric population indication.
- In May 2022, Breakthrough Therapy Designation was granted.

2.6 Other Relevant Background Information

N/A

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The BLA was submitted electronically and formatted as an electronic Common Technical Document according to FDA guidance for electronic submission. This submission consisted of the five modules in the common technical document structure. It was adequately organized and integrated to conduct a complete clinical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Four Bioresearch Monitoring clinical investigator inspection assignments were issued with the original BLA. The clinical study sites were selected based on subject enrollment, previous inspection history, and the data and information submitted in BLA 125771/0. No significant objectionable inspectional findings were reported.

No additional sites were inspected as part of this sBLA review.

3.3 Financial Disclosures

Complete financial disclosures were provided for the studies and reviewed. No significant financial interests or conflicts that could potentially bias the conduct of the study were identified. A complete list of clinical investigators and sub-investigators was provided and reviewed.

Covered clinical study (name and/or number):
Was a list of clinical investigators provided? X Yes ☐ No (Request list from applicant)
Total number of investigators identified: 137
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): 6
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: 0 Significant payments of other sorts: 6 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0 Is an attachment provided with details of the disclosable financial interests/arrangements? X Yes ☐ No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? X Yes ☐ No (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0

Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant) N/A

Reviewer Comment: *There were six investigators who received significant payments for general consulting, registration and speaker fees, travel, and accommodation. The details of the disclosable arrangements were provided. However, the Applicant did not specifically describe the steps taken to minimize potential bias. Most of the compensation to investigators was used for travel, consultations, and educational events. The clinical reviewer doesn't have any concerns regarding trial conduct or outcome as no specific concerns arose from review of site-specific data.*

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

4.1 Chemistry, Manufacturing, and Controls

BIVV001 is a fully recombinant fusion protein comprising a single-chain beta domain deleted analogue of human FVIII covalently fused to the Fc domain of human immunoglobulin G1, the FVIII-binding D'D3 domain of human VWF, and 2 XTEN polypeptides.

There were no significant issues related to chemistry, manufacturing, and controls (CMC) that were identified that would preclude approval.

Please refer to the original BLA CMC memorandum for details.

4.2 Assay Validation

Required validation of applicable methods and their controls for FVIII assays have been completed and no issues were identified. FVIII plasma activity was measured by two different assays: the one-stage clotting assay and chromogenic assay. The review primarily utilized the one-stage clotting assay as this was the most conservative of the assays.

4.3 Nonclinical Pharmacology/Toxicology

PK and toxicokinetic assessments were performed following single and repeat intravenous (IV) administrations of BIVV001 in HA mice, (b) (4) rats, and (b) (4) monkeys. Systemic exposure levels after a single administration of BIVV001 in mice, rats, and monkeys showed a dose-dependent proportional increase in maximum concentration and area under the concentration-time curve. The terminal half-life of BIVV001, which reflects the exposure and clearance of the fusion protein in plasma, was approximately 30 hours in mice and monkeys and approximately 20 hours in rats.

The no-observed-adverse-effect level was the maximum dose level administered, 750 IU/kg/dose, which is 15-fold higher than the maximum recommended prophylactic clinical dose level of BIVV001 (50 IU/kg once weekly). No significant issues were identified that raise safety concerns.

Please refer to the original BLA Pharmacology/Toxicology review for complete details.

4.4 Clinical Pharmacology

BIVV001 temporarily replaces the missing FVIII needed for effective hemostasis. BIVV001 has demonstrated 3- to 4-fold prolonged half-life relative to other standard and extended half-life FVIII products.

4.4.1 Mechanism of Action

BIVV001 is a rFVIII analogue fusion protein that is independent of endogenous VWF, thereby overcoming the half-life limit imposed by FVIII-VWF interactions. The D'D3 domain of VWF is the region that interacts with FVIII. Appending the D'D3 domain of VWF to a rFVIII-Fc fusion protein provides protection and stability to FVIII and prevents FVIII interaction with endogenous VWF, thus overcoming the limitation on FVIII half-life imposed by VWF clearance.

The Fc region of human immunoglobulin G1 binds to the neonatal Fc receptor, part of a naturally occurring pathway that delays lysosomal degradation of immunoglobulins by recycling them back into circulation, thus prolonging the plasma half-life of the fusion protein.

BIVV001 contains 2 XTEN polypeptides that alter the hydrodynamic radius of the fusion protein, thus reducing rates of clearance and degradation and improving PK properties. In BIVV001, the natural FVIII B domain (except 5 amino acids) is replaced with the first XTEN, inserted in between FVIII N745 and E1649 amino acid residues; the second XTEN is inserted in between the D'D3 domain and Fc.

4.4.2 Human Pharmacodynamics

Administration of BIVV001 increases plasma levels of FVIII, temporarily correcting the coagulation defect in patients with HA.

4.4.3 Human Pharmacokinetics

The PK parameters were based on plasma FVIII activity measured by the activated partial thromboplastin clotting time-based one-stage clotting assay.

A once-weekly dose of BIVV001 at 50 IU/kg provided FVIII activity in the normal to near-normal range (>40 IU/dL) for 2 to 3 days, >10 IU/dL for approximately 6 to 7 days, and in the mild hemophilia range (>5 IU/dL) at the end of the weekly dosing interval in both cohorts of children <12 years of age.

Evaluation of the PK/PD data for BIVV001 supported the recommended dose of 50 IU/kg in both adults and children. Please refer to Clinical Pharmacology review memorandum for complete details.

4.5 Statistical

The statistical reviewer verified that the primary endpoint analyses and key secondary endpoints cited by the Applicant were supported by the submitted data. 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. Please refer to Biostatistics Review memorandum for details.

4.6 Pharmacovigilance

No postmarketing requirements or commitments will be planned post approval. There is an ongoing voluntary study to assess safety of use of BIVV001 in previously untreated patients and an ongoing long-term follow-up study of clinical trial subjects.

Please refer to the original BLA Office of Biostatistics and Epidemiology memorandum for details.

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

5.1 Review Strategy

Clinical trials that provided evidence for safety and efficacy of BIVV001 were conducted under IND 17464. Data from the completed pediatric study (Study EFC16295) served as the primary basis for review. Analyses were performed using JMP 16 to reproduce key efficacy and safety analyses based on the submitted datasets and to conduct additional exploratory analyses.

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

Documents pertinent to this review were provided in BLA125771/136 and IND 17464, including the overview, analyses datasets, clinical summary, and clinical study reports.

5.3 Table of Studies/Clinical Trials

An overview of the clinical trial is presented in Table 3 below.

Table 3. Study Report Pertinent to Claimed Indication, Study EFC16295

Parameter	Value
Type of study	Safety, efficacy, and PK
Study identifier	EFC16295/XTEND-Kids
Location of study report	Module 5.3.5.2
Coordinating investigator (center)	Lynn M. Malec, MD, MSc (Medical College of Wisconsin, USA)
Number of centers	40 active centers
Objective(s) of study	Primary: to evaluate the safety of BIVV001 in previously treated patients <12 years of age with severe Hemophilia A
Study design and type of control	A multinational, multicenter open-label, Phase 3 trial
Test product(s)	BIVV001
Formulation	Lyophilized powder in a sterile vial that requires reconstitution with Sterile Water for Injection
Dosage regimen	50 IU/kg once weekly
Route of administration	Intravenous injection
Reference Therapy	N/A
Formulation	N/A
Dosage regimen	N/A
Route of administration	N/A

Parameter	Value
Number of study participants	
Total	74[a]/72[b]
Gener[a] (male/female)	74/0
Race[a]	Caucasian: 55; Black: 3; Other: 4; Asian: 8; Not reported due to privacy regulations: 4
Age[a], mean ± SD (range)	5.99 ± 2.91 (1.4-11)
Treatment group[a]	All participants were treated with BIVV001 once-weekly prophylaxis
Healthy study participants or diagnosis of study participants	Previously treated patients <12 years of age with severe Hemophilia A
Duration of treatment	52 weeks
Study status	Complete
Type of report	Full

Source: Tabular Listing of Clinical Studies BLA 125771 Module 5.2.
a. Treated
b. Completed study drug according to investigator (end-of-treatment form).
Abbreviations: CSR, clinical study report; PK, pharmacokinetics; N/A, not applicable; SD, standard deviation.

5.4 Consultations

No internal FDA consultants were requested by the clinical team during the review of this sBLA.

5.4.1 Advisory Committee Meeting (if applicable)

An advisory committee meeting was not convened because the biologic is not the first in its class. Additionally, the design of the clinical study is similar to studies conducted to support other approved products and the review of the application did not raise significant safety or efficacy concerns that would warrant a public discussion and could not be addressed through information in the label. Consultative expertise was not required, and no public health concerns arose upon review of this file.

5.4.2 External Consults/Collaborations

There were no external consults or collaborations that were requested by the clinical reviewer in the review of this BLA.

5.5 Literature Reviewed

1. Calvez, T, H Chambost, S Claeyssens-Donadel, R d'Oiron, V Goulet, B Guillet, V Heritier, V Milien, C Rothschild, V Roussel-Robert, C Vinciguerra, J Goudemand, and N FranceCoag, 2014, Recombinant factor VIII products and inhibitor development in previously untreated boys with severe hemophilia A, Blood, 124(23):3398-3408.
2. Collins, PW, BP Palmer, EA Chalmers, DP Hart, R Liesner, S Rangarajan, K Talks, M Williams, CR Hay, and UKHCD Organization, 2014, Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe hemophilia A, 2000-2011, Blood, 124(23):3389-3397.
3. Fischer, K, R Lassila, F Peyvandi, G Calizzani, A Gatt, T Lambert, J Windyga, A Iorio, E Gilman, M Makris, and E participants, 2015, Inhibitor development in haemophilia according to concentrate. Four-year results from the European HAemophilia Safety Surveillance (EUHASS) project, Thromb Haemost, 113(5):968-975.

4. Gouw, SC, HM van den Berg, K Fischer, G Auerswald, M Carcao, E Chalmers, H Chambost, K Kurnik, R Liesner, P Petrini, H Platokouki, C Altisent, J Oldenburg, B Nolan, RP Garrido, ME Mancuso, A Rafowicz, M Williams, N Clausen, RA Middelburg, R Ljung, JG van der Bom, PedNet, and IdSG Research of Determinants of, 2013, Intensity of factor VIII treatment and inhibitor development in children with severe hemophilia A: the RODIN study, Blood, 121(20):4046-4055.
5. Soucie, JM, CH Miller, B Dupervil, B Le, and TW Buckner, 2020, Occurrence rates of haemophilia among males in the United States based on surveillance conducted in specialized haemophilia treatment centres, Haemophilia, 26(3):487-493.
6. Vezina, C, M Carcao, C Infante-Rivard, D Lillicrap, AM Stain, E Paradis, J Teitel, GE Rivard, C Association of Hemophilia Clinic Directors of, and C of the Canadian Association of Nurses in Hemophilia, 2014, Incidence and risk factors for inhibitor development in previously untreated severe haemophilia A patients born between 2005 and 2010, Haemophilia, 20(6):771-776.

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1

Study EFC16295: A Phase 3 Open-Label, Multicenter Study of the Safety, Efficacy, and Pharmacokinetics (PK) of Intravenous (IV) BIVV001 in Previously Treated Pediatric Patients <12 Years of Age With Severe Hemophilia A

6.1.1 Objectives (Primary, Secondary, etc.)

The primary objective was to evaluate safety in previously treated pediatric subjects.

Key secondary objectives include efficacy evaluation of BIVV001 as a prophylaxis treatment and in the treatment of bleeding episodes, consumption, the effect of joint health outcomes, perioperative management, and quality of life outcomes.

6.1.2 Design Overview

Subjects were in two age cohorts (<6 years of age and 6 to <12 years of age) and received BIVV001 for approximately 52 weeks to reach 50 exposure days (EDs). PK evaluation was performed on a subset of subjects.

6.1.3 Population

The study population included PTPs <12 years of age with severe HA (defined as <1 IU/dL [<1%] endogenous FVIII or a documented genotype known to produce severe HA). 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

The study is comprised of two age cohorts (<6 years of age and 6 to <12 years of age), and subjects received IV BIVV001 at a dose of 50 IU/kg once weekly for 52 weeks.

6.1.5 Directions for Use

Prophylaxis treatment with 50 IU/kg was given once weekly. During a bleeding episode, a single dose was administered with additional and adjusted doses given every two to three days if the bleeding episode did not improve. For minor bleeds, a decreased dose of 30 IU/kg could be given.

For perioperative use, a dose of 50 IU/kg was given.

Reviewer Comment: *Please refer to the Clinical Pharmacology review for further details on pediatric dosing and clearance. Although higher clearance was noted in the pediatric population, dosing was not adjusted as the clinical endpoint of ABR remained adequate.*

6.1.6 Sites and Centers

The study was conducted worldwide in 15 countries/regions (USA, Canada, France, Germany, Hungary, Ireland, Italy, Netherlands, Spain, Sweden, Switzerland, UK, Turkey, Australia, and Taiwan).

6.1.7 Surveillance/Monitoring

The trial was conducted in accordance with Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice. The 21 Code of Federal Regulations, parts 312, 50, and 56 were followed.

The study employed an Independent Data Monitoring Committee.

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint is the occurrence of inhibitor development (neutralizing antibodies directed against FVIII as determined via the (b) (4) Bethesda assay). Inhibitor development was defined as an inhibitor result of ≥0.6 BU/mL that is confirmed by a second test result from a separate sample, drawn two to four weeks following the date when the original sample was drawn.

The key secondary endpoints included ABR for treated bleeding episodes and all bleeding episodes; percentage of subjects who maintain FVIII activity levels over 1%, 3%, 5%, 10%, 15% and 20% at Day 7; and the number of injections/doses to treat a bleeding episode.

Reviewer Comment: *Evaluation of ABR for treated and untreated bleeds were included in the label.*

6.1.9 Statistical Considerations & Statistical Analysis Plan

The efficacy endpoint of ABR was analyzed using the full analysis set, including subjects with an efficacy period of at least 26 weeks or 50 EDs. 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.

Reviewer Comment: *Although treated bleeds are informative, all bleeds (treated and untreated) give a comprehensive ABR of a subject and were analyzed as the primary endpoint by this reviewer and will be included in the label.*

6.1.10 Study Population and Disposition

The full analysis set is comprised of all subjects who received at least one dose of BIVV001. The per protocol set are all subjects evaluated for the efficacy endpoint.

There were 79 subjects screened. Five were failures due to a history of inhibitors or did not meet the criteria to understand the purpose and risks of the study; 74 subjects received at least one dose of BIVV001.

Major protocol deviations were noted in 31 subjects and related to study visits that were not performed, questionnaires that were incomplete, and failures to report requested safety events within a protocol-specified time window. None of these impacted the efficacy evaluation.

6.1.10.1 Populations Enrolled/Analyzed

At study entry, 71 (95.9%) of the 74 enrolled subjects had a historical documented FVIII activity level below 1% and the remaining 3 subjects had FVIII levels below 1% at screening visit and a documented genotype known to produce severe HA.

6.1.10.1.1 Demographics

As per Section 1.1.

Table 4. Demographics, Study EFC16295

Patient Age	**<6 Years**	**6 to <12 Years**
N	38	36
Male, n (%)	38 (100)	36 (100)
Race, n (%)		
Not reported	0	4 (11.1)
White	30 (78.9)	25 (69.4)
Black	1 (2.6)	2 (5.6)
Asian	4 (10.5)	4 (11.1)
Other	3 (7.9)	1 (2.8)
Ethnicity, n (%)		
Hispanic/Latino	2 (5.3)	1 (2.8)
Age		
Mean (SD)	3.7 (1.2)	8.4 (2.1)
Median (min, max)	4 [1.4,5]	8 [6, 11]

Source: Adapted from CSRXXX
Abbreviations: max, maximum; min, minimum; SD, standard deviation.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

There were 71 subjects with a historical documented FVIII activity level below 1% and the remaining 3 had FVIII levels below 1% at screening and documented genotype. More than half of the subjects had genotypes associated with inhibitor development to FVIII such as confirmed intron 22 inversions (16 subjects; 21.6%), large structural change (>50 bp, including intron 1, 11; 14.9%), and frameshift (8; 10.8%), missense (7; 9.5%), and nonsense (4; 5.4%) mutations. The majority of the subjects (57; 77.0%) had no family history of an inhibitor. No participant was HIV, HBV, or HCV positive.

The majority (81.1%) had prior exposure to rFVIII and the remaining subjects to plasma derived FVIII. All subjects had >50 EDs and those in the 6 to 12 years of age cohort had over 150 EDs. One subject was on an on-demand regimen. All others were on

prophylactic treatment prior to study entry and were receiving therapy two to three times weekly. The mean age at the start of first prophylactic treatment was one year.

The mean (SD) number of bleeding episodes in the 12 months prior to study was 2.1 (4.2). Twenty-seven (38.6%) reported no bleeding episodes and 39 (55.7%) reported 1 to 5 bleeding episodes. One subject (<6 years of age) had 11 joint bleeding episodes and one subject (6 to <12 years of age) had 32 bleeding episodes (30 joint bleeds; 7 were traumatic). Two subjects had three target joints at baseline.

Please see Table 5 below for bleeding episodes 12 months preceding study entry.

Table 5. Bleeding Rate 12 Months Preceding Study Entry

Variable	ABR
Total bleeding episodes, n=70	
Mean (SD)	2.1 (4.2)
Median (min; max)	1.0 (0; 32)
Joint bleeding episodes, n=66	
Mean (SD)	(3.9)
Median (min; max)	0 (0; 30)
Spontaneous bleeding episodes, n=63	
Mean (SD)	0.6 (2.9)
Median (min; max)	0 (0; 23)
Traumatic bleeding episodes, n=59	
Mean (SD)	0.5 (1.3)
Median (min; max)	0 (0; 7)

Source: Adapted from BLA 125771/136 Clinical Study Report page 31
Abbreviations: ABR, annualized bleeding rate; max, maximum; min, minimum; SD, standard deviation.

6.1.10.1.3 Subject Disposition

All 74 subjects received at least one dose of BIVV001; 72 subjects completed the study. Two subjects prematurely discontinued, one each due to baseline inhibitor and one due to fear of blood draws.

6.1.11 Efficacy Analyses

Of the 74 subjects who received one dose, the majority (66, 89.2%) achieved more than 50 EDs; 73 subjects were treated for at least 39 weeks and 56 subjects were treated for at least 52 weeks. There were 8 subjects that did not reach 50 EDs and 7 had over 26 weeks of exposure.

Reviewer Comment: *In the review of previously approved FVIII products, a minimum of 52 weeks follow-up or at least 50 EDs was required to evaluate safety and efficacy. With extended half-life products, it is reasonable for subjects to be evaluated with at least 26 weeks of exposure. Those subjects that did not meet 50 EDs had at least 26 weeks of exposure, except one subject who will not be efficacy evaluable as they only had 3 EDs and positive inhibitor at baseline and should have been excluded from the study.*

6.1.11.1 Analyses of Primary Endpoint(s)

The primary endpoint was the occurrence of inhibitor development. See Section 6.1.12 for the Safety Analysis.

6.1.11.2 Analyses of Secondary Endpoints

The mean (SD) dosing interval during the efficacy period was 7 days (0.08) with mean weekly dose of 55 (4.3). Of the 61 subjects who had trough levels within 168 ± 5 hours (7 days) from previous dose, all subjects had a level over 3%. The majority (86.9%) had a trough of over 5%.

The efficacy of BIVV001 weekly prophylaxis was estimated by the mean ABR and 2-sided 95% CI using a negative binomial model.

Of the 74 subjects, 47 (63.5%) had an ABR of 0 and 25 (33.8%) had an ABR of >0 to 5 for treated bleeds. There were two subjects in the 6 to <12 years of age cohort who had high ABRs >5 and are described below.

Of the 74 subjects, 37 had an ABR of 0 for all bleeding episodes (treated and untreated) and 3 subjects had an ABR >20. One of these subjects is described below for a high number of treated bleeds. The other two subjects had a high number of untreated bleeds, which included skin, muscle, and mucosal bleeds.

Subject (b) (6)

Subject (b) (6) had an ABR rate of 2 which included a traumatic bleed prior to study entry. On the study, this subject had a high ABR rate of 21.4 (3 traumatic joint bleeds and one spontaneous bleed). This subject did not receive weekly prophylaxis treatment due to traumatic joint bleeds and received BIVV001 at 2.6 IU/kg two to three times a week for a total of four months. He received a total of 33 BIVV001 injections between Day 48 and Day 169 for a hip bleed on Day 48 and Day 81. On Day 136, the subject had a spontaneous bleed in his joint. He subsequently had a traumatic wrist bleed on Day 340. After the initial doses to treat the bleed were administered, the investigator decided to continue treatment with an intensive consolidation regimen every two to three days. On Day 136, the subject reported left hip pain, without signs of bleeding or joint damage on Day 142 by MRI. As per the statistical analysis plan, injections to treat a bleeding episode taken >72 hours after the preceding treatment were considered to treat a new bleed. Therefore, the consolidated time frame of treatments resulted in 18 “new” treated bleeds. Predose FVIII levels were consistently above 50IU/dL. This subject did not develop any inhibitors or antidrug antibodies (ADAs).

Subject (b) (6)

Subject (b) (6) had an ABR of 3 prior to study entry and ABR of 5.1 while on therapy. This Subject had five total treated bleeding episodes; all were traumatic bleeds. There were four traumatic joint bleeds and one oral bleed. All join bleeds occurred five to seven days after the previous prophylactic injection and were treated with one dose.

Reviewer Comment: *The consolidated treatment regimen of Subject* (b) (6) *resulted in 18 “new” bleeds, although the treatment was to resolve and maintain the 2 traumatic bleeding events. This subject did have one spontaneous bleed while on the treatment regimen which is odd since his FVIII levels were maintained above 50%. It is unclear if this was a true event as the MRI did not show signs of bleeding and therefore reassuring that this spontaneous bleed may not have been a true event. Including data from this subject in a table to assess the total ABR will not be informative to prescribers since this subject was not on the prescribed dosing regimen and the ABR had been*

inflated since he remained on twice a week prophylaxis therapy. The mean ABR for treated bleeds changes from 0.8 to 1.3 bleeds/year with the inclusion of this subject in the 6 to <12 years of age cohort and the overall mean ABR for treated bleeds changes from 0.6 to 0.9 bleeds/year. For all bleeds, the mean ABR changes from 2.3 to 2.9 bleeds/year with the inclusion of this subject in the 6 to <12 years of age cohort and the overall mean ABR for all bleeds changes from 2.6 to 2.8 bleeds/year.

For other products, the reviewer has included those subjects with high bleed rates to inform that a dosing regimen may not be beneficial to all subjects (subjects were on the prescribed dosing regimen), so this subject should be described briefly in the package insert as part of the subjects who completed 26 weeks but not included in the efficacy evaluable population.

One subject who had an inhibitor at baseline and only had three EDs was not included in the efficacy evaluable population.

Table 6. ABR in Efficacy Evaluable Subjects With an Efficacy Period >26 Weeks

Endpoint	<6 Years n=37	6 to <12 Years n=35	Overall N=72
Bleeding episodes	17	47	64
Mean (95 % CI)	2.8 (1.4, 5.6)	2.3 (1.3, 4.1)	2.6 (1.6, 4.0)
Median (Q1; Q3)	0 (0; 2.0)	1 (0, 2.9)	0.5 (0, 2.1)
Treated Joint bleeding episodes			
Mean (SD)	0.2 (0.1, 0.6)	0.4 (0.2, 0.9)	0.3 (0.2, 0.6)
Median (min; max)	0 (0; 0)	0 (0; 0)	0 (0; 0)
Spontaneous bleeding episodes			
Mean	0.2 (0.1, 0.4)	0.2 (0.1, 0.6)	0.2 (0.1, 0.3)
Median (min; max)	0 (0; 0)	0 (0; 0)	0 (0; 0)

Source: Adapted from BLA 125771/136 Clinical Study Report page 40; FDA Adjudicated
Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; max, maximum; min, minimum.

The majority (87.8%) of subjects had no spontaneous bleeds. There were 11 subjects with spontaneous bleeding events. There were 31 subjects with traumatic bleeding events. The mean (SD) spontaneous ABR rate was 0.15 (0.44). The mean (SD) traumatic ABR rate was 0.42 (0.91). Joints were the most common location for treated bleeds. The majority (82.4%) of subjects reported no joint bleeds.
There were two subjects with 3 target joints at baseline. Both subjects had one target joint resolve.

Reviewer Comment: *Joint bleeding was the most common location for treated bleeds, as expected. The low spontaneous bleeding rate is reassuring with this product. It is unclear if subjects were more active with this extended half-life product and therefore had traumatic bleeds. The traumatic bleeds rate is <1 which is reasonable.*

The majority (81.3%) of bleeding episodes were controlled by a single injection. All bleeding episodes were controlled with <2 injections, except two requiring four injections, which occurred in the same subject (Subject (b) (6)). Only the first injections were evaluated for response with the majority (97.5%) rated as excellent or good.
The majority (53; 87%) of subjects maintained FVIII levels >5% (pre-dose trough level based on a one-stage assay).

Surgery

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.

Subject (b) (6) : Dental Restoration (7 Teeth)/Tooth Extraction
FVIII level was 32.7%. Prior to the surgery, a loading dose of 61.9 IU/kg BIVV001 was administered. The hemostasis was rated as excellent by the Investigator. There was no blood loss during the surgery or postoperative. The study participant did not receive any other FVIII treatment or blood components for the surgery. On Day 1 post-surgery, FVIII activity level was 102.3%. On Day 2 post-surgery, an additional dose of 37.1 IU/kg was administered. The weekly dosing regimen of 50 IU/kg was resumed on Day 4 post-surgery.

Subject (b) (6) : Circumcision
FVIII activity level on the day of surgery was 59.5% (prior prophylactic dose was administered two days beforehand). Prior to the surgery, a loading dose of 60.4 IU/kg BIVV001 was administered. The hemostasis was rated as excellent by the investigator. Estimated blood loss during surgery was 50 mL and there was 10 mL of postoperative blood loss. The study participant did not receive any other FVIII treatment or blood components for the surgery. On Day 1 post-surgery, FVIII activity level was 179.1% and the study participant was discharged from the hospital. The weekly dosing regimen of 50 IU/kg was resumed on Day 6 post-surgery.

There were 9 minor surgeries reported where a preoperative loading dose was sufficient to maintain hemostasis.

Reviewer Comment*: These numbers were updated in the package insert. The Applicant confirmed that 14 major surgeries in 13 subjects and 27 minor surgeries in 23 subjects occurred across both adult and pediatric studies.*

6.1.11.3 Subpopulation Analyses

There were two subjects with a total of three target joints at baseline. The older cohort subject had two target joints, and both resolved at a year. The <6-years-of-age subject could not be evaluated since they did not have at least 12 months of exposure.

6.1.11.4 Dropouts and/or Discontinuations

Two subjects discontinued. One each due to fear of blood draws and a positive low titer inhibitor at baseline. As this subject was determined to no longer meet eligibility criteria, he was withdrawn from the study after receiving three doses. A subsequent test result was negative.

6.1.11.5 Exploratory and Post Hoc Analyses

The Hemophilia Joint Health Score was used in subjects above 4 years of age. The change from baseline at Week 26 and Week 53 was -0.1 and -0.6, respectively. Quality of life data were collected at baseline, Week 26, and Week 52 in subjects 4 to 7 years of age, in subjects 8 to <12 years of age, and in respective caregivers via 4 separate Haemo-QoL questionnaires. The mean change from baseline at Week 26 and Week 52 was -3.46 and -2.85.

Reviewer Comment: *As discussed in the original BLA, these measurements were evaluated by the Center for Drug Evaluation and Research patient-reported outcome team.*

The open-label nature of the XTEND-1 study (Study EFC16293; NCT04161495) design may have led to biased responses for the patient-reported outcome measures (i.e., patients' knowledge of treatment assignment is likely to influence how they report information on the patient-reported outcome) and, subsequently, to biased estimates of treatment effect.

The data are challenging to interpret given identified limitations in the context of a single-arm study. Although the data may appear promising, there is uncertainty in the results as they may be biased. This data will not be included in the label.

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety was evaluated in all subjects who received at least one dose of BIVV001. The primary endpoint of this study was the occurrence of inhibitor development to FVIII.

6.1.12.2 Overview of Adverse Events

Of the 74 subjects, 62 experienced a total of 227 treatment-emergent adverse events (TEAEs). The above TEAEs were graded as mild, moderate, or severe. Of the 227 TEAEs that occurred, the majority (196, 86%) were graded mild.

No TEAEs resulted in death or led to treatment discontinuation.

The most common TEAEs reported in >5% of patients were upper respiratory tract infection (11 subjects; 14.9%), gastroenteritis viral and nasopharyngitis (6 subjects each; 8.1%), viral infection and viral upper respiratory tract infection (4 subjects each; 5.4%), head injury (6 subjects; 8.1%), contusion (5 subjects; 6.8%), vomiting (5 subjects; 6.8%), diarrhea (4 subjects; 5.4%), pyrexia (10 subjects; 13.5%), SARS-CoV-2 test positive (11 subjects; 14.9%), arthralgia and pain in extremity (5 subjects each; 6.8%).

Reviewer Comment*: The above AEs were analyzed from the ADAE dataset. ADRs with frequency of >3% were reported for Altuviiio in the label for all the subjects in the adult, adolescent, and pediatric studies. SARS-COV-2, viral infections, upper respiratory tract infections, nasopharyngitis and contusions were not included.*

There were no clinically meaningful TEAEs between the two age cohorts.

6.1.12.3 Deaths

There were no deaths in the pediatric subjects.

6.1.12.4 Nonfatal Serious Adverse Events

There were 10 SAEs reported in 9 subjects (5 in the <6 years of age and 4 in 6 to <12 years of age cohorts). There were 5 SAEs that were severe including circumcision, bacteremia, vascular device occlusion, head injury, and eosinophilic esophagitis. These were not related to the study product.

***Reviewer Comment**: This reviewer agrees that these sever events were not related to the study product.*

6.1.12.5 Adverse Events of Special Interest

Inhibitor development did not occur in any of the subjects. One subject had a positive low tier FVIII inhibitor at baseline prior to exposure to BIVV001.

There were three subjects who had ADAs at baseline before receiving BIVV001. The titers were 20, 40, and 80, respectively. One subject was positive against Fc, one was against FVIII, and one was negative against all tested domains.

There were no reports of Grade 3 or higher serious allergic reaction or anaphylaxis. There were no vascular thrombotic events. There were no reports of overdose.

***Reviewer Comment:** There were no reports of inhibitors in this PTP population as most have crossed the threshold of 10 to 15 EDs with BIVV001. It is unclear why there is a presence of ADAs prior to treatment. It is reassuring that these antibodies are transient and have no clinical effect.*

6.1.12.6 Clinical Test Results

There were no clinically meaningful patterns or trends observed in hematologic parameter changes over time in either age cohort. There were no clinically meaningful patterns or trends observed in chemistry parameter changes over time in either age cohort. There were no clinically meaningful patterns or trends observed in von Willebrand panel changes over time in either age cohort.

6.1.12.7 Dropouts and/or Discontinuations

A total of 72 subjects completed the study and 2 subjects discontinued.

One subject discontinued due to fear of blood draw and one with a positive low titer FVIII inhibitor test at baseline.

***Reviewer Comment:** Subject (b) (6) was found to have a positive inhibitor at baseline and had a 1-week period with three EDs. Subject (b) (6) discontinued due to fear of blood draws but completed 42 weeks on study with 44 EDs.*

6.1.13 Study Summary and Conclusions

The results from this study show that once-weekly IV BIVV001 at 50 IU/kg was well tolerated and effective as routine prophylaxis to protect against bleeding episodes in PTPs <12 years of age with severe HA. In addition, BIVV001 was effective for the control of bleeding episodes and provided hemostatic efficacy during a surgical procedure. The most commonly reported AEs were pyrexia and upper respiratory tract infections and were mild and transient. There were no inhibitors detected thus far and no new safety signals in the pediatric population. Overall, the available data support the use of BIVV001 in pediatric patients with HA.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

The efficacy evaluation was based on the pediatric study. Therefore, an integrated summary of efficacy was not conducted.

7.1.1 Methods of Integration

N/A

7.1.2 Demographics and Baseline Characteristics

See Section 1.1.

7.1.3 Subject Disposition

See Section 6.1.10.

7.1.4 Analysis of Primary Endpoint(s)

As above.

7.1.5 Analysis of Secondary Endpoint(s)

As above.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The safety evaluation was based on the pediatric study.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The safety dataset included all subjects who received at least one dose of BIVV001, which included subjects from the pediatric study.

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

There were no deaths in the pediatric study.

8.4.2 Nonfatal Serious Adverse Events

There were no serious AEs reported in the pediatric study that were attributed to the study product.

8.4.3 Study Dropouts/Discontinuations

As above.

8.4.4 Common Adverse Events

The most common AEs (>10%) were upper respiratory tract infection and pyrexia.

8.4.5 Clinical Test Results

Overall, no clinically relevant changes associated with exposure to BIVV001 have been observed for laboratory parameters.

8.4.6 Systemic Adverse Events

See individual study sections.

8.4.7 Local Reactogenicity

N/A

8.4.8 Adverse Events of Special Interest

No subjects were reported to have developed FVIII inhibitors.

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)

As above.

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

8.6 Safety Conclusions

The most commonly reported AEs were mild and transient. No FVIII inhibitor development was observed in the safety-evaluable population. No deaths related to BIVV001 occurred. No anaphylactic allergic reactions related to BIVV001were observed and no clinical consequence of ADAs were noted.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Based on the rare occurrence of HA in women, experience regarding the use of FVIII during pregnancy and breastfeeding is not available.

9.1.2 Use During Lactation

N/A

9.1.3 Pediatric Use and PREA Considerations

This application is exempt from PREA because it is intended for a biologic product for which orphan designation has been granted.

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

Overall, BIVV001 continued to demonstrate efficacy in children for on-demand treatment to control bleeding episodes, perioperative management of bleeding, and routine prophylaxis.

No treatment-related deaths were observed. No new safety signals were observed in the safety-evaluable pediatric subjects.

FVIII inhibitors and allergic reactions will be communicated in the Warnings and Precautions sections of the label as potential risks.

The safety and efficacy of BIVV001 has been demonstrated for the following indications in adults and children:

- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 7. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hemophilia A is a rare hereditary bleeding disorder characterized by recurrent bleeding which, if untreated, leads to synovitis, chronic arthropathy, muscular atrophy, and deformities. • Treatment of bleeds may delay these complications but does not prevent them. • Primary prophylaxis with regular FVIII injections initiated at an early age is now the standard of care for patients with severe hemophilia A. • The frequency of bleeding in hemophilia A is generally inversely correlated with the FVIII activity level.	• Hemophilia A is a hereditary, serious, and life-threatening disease. • Hemophilia A can have a debilitating impact on physical and psychosocial well-being.
Unmet Medical Need	• There are several FVIII products licensed by FDA, both recombinant and plasma derived. • Plasma-derived products carry a potential risk of transmission of infection; all products carry the risks of inhibitor formation leading to ineffective therapy and hypersensitivity.	• Development of products with greater incremental recovery, good hemostatic coverage, and extended half-life is desirable. • Less frequent injections may reduce the burden of treatment.
Clinical Benefit	• BIVV001 has demonstrated an extended half-life. • One trial to evaluate the efficacy of BIVV001 in children was provided. The efficacy was demonstrated for treatment of and prevention of bleeding events in patients with hemophilia A. • BIVV001 was effective in the perioperative setting for reduction of bleeding during surgery.	• The evidence for clinical benefit is shown in reduction of bleeds.
Risk	• The identified risks of FVIII replacement therapy are the development of FVIII inhibitors, thrombosis, and allergic reactions. • In the clinical trials, no previously treated patient developed FVIII inhibitors. • No Grade 3 or higher hypersensitivity reactions were reported.	• The risk of inhibitor development and allergic reactions is comparable to other FVIII products. • BIVV001 was well tolerated with no unexpected safety issues.
Risk Management	• The most substantial risks of treatment with BIVV001 are the development of FVIII inhibitors and hypersensitivity.	• The package insert and routine pharmacovigilance activities are adequate to manage risk.

Source: FDA Clinical Reviewer
Abbreviations: FDA, U.S Food and Drug Administration; FVIII, coagulation factor VIII

11.2 Risk-Benefit Summary and Assessment

The overall benefit-risk profile of BIVV001 remains favorable for approved use in adults and children with HA for routine prophylaxis to reduce the frequency of bleeding episodes; on-demand treatment and control of bleeding episodes; and perioperative management of bleeding.

The benefits of BIVV001 include:

- On-demand BIVV001 is effective for treatment and prevention of spontaneous or traumatic bleeding in patients with HA
- BIVV001 is effective in the perioperative setting for reduction of bleeding during surgery. BIVV001 demonstrated clinical benefit in all age groups for routine prophylaxis.

The risks of BIVV001 include:

- FVIII thrombotic event development and potential hypersensitivity reactions. The risk of development of thrombosis is considered an expected AE.

11.3 Discussion of Regulatory Options

The available data remains favorable to support the labeling changes to update the clinical efficacy and safety data for the indication for on-demand treatment and control of bleeding episodes, perioperative management, and routine prophylaxis for children with HA.

11.4 Recommendations on Regulatory Actions

Recommendation of approval to the updates to the USPI to include the completed pediatric study results.

The approved indication for the on-demand treatment and control of bleeding episodes, perioperative management, and routine prophylaxis indications for adults and children with HA remains unchanged.

11.5 Labeling Review and Recommendations

The revised package insert was reviewed, commented on, and revised by the appropriate discipline reviewers. FDA's Advertising and Promotional Labeling Branch conducted its review from a promotional and comprehension perspective. Labeling issues have successfully been resolved with the Applicant.

Key changes included:

- deleting all extension study data
- revising the efficacy data presented for the pediatric efficacy evaluable population
- updating the safety section with data from the adult, adolescent, and pediatric data
- updating the perioperative section

11.6 Recommendations on Postmarketing Actions

No postmarketing requirement or postmarketing commitment studies are requested at this time. Review of the clinical data found no safety concern that would necessitate a Risk Evaluation and Mitigation Strategy, a postmarketing commitment, or a required postmarketing study that is specifically designed to evaluate safety as a primary endpoint.