

Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

Application Type	BLA Supplement
STN	125426/223
CBER Received Date	May 24, 2023
PDUFA Goal Date	March 22, 2024
Division / Office	DCEGM/OCE/OTP
Committee Chair	Christine Knoll, MD
Clinical Reviewer(s)	Christine Knoll, MD
Project Manager	Catherine Tran, MS
Priority Review	Standard
Reviewer Name(s)	Jingyi Zhai, Ph.D. Visiting Associate, TEB2/DB/OBPV
Supervisory Concurrence	Lin Huo, Ph.D., Team Lead, TEB2/DB/OBPV
	Lihan Yan, Ph.D., Branch Chief, TEB2/DB/OBPV
Applicant	Medexus Pharma, Inc.
Established Name	Coagulation Factor IX (Recombinant)
(Proposed) Trade Name	IXINITY
Pharmacologic Class	Coagulation factor
Formulation(s), including Adjuvants, etc	Power (and solvent) for solution for injection
Dosage Form(s) and Route(s) of Administration	Lyophilized white or almost white powder, in single-use glass vials containing nominally 250, 500, 1000, 1500, 2000, or 3000 international units (IU) per vial; Intravenous injection
Dosing Regimen	For intravenous use after reconstitution only. <ul style="list-style-type: none"> • On-demand treatment and control of bleeding episodes and perioperative management of bleeding: <ul style="list-style-type: none"> - Adolescents/Adults (≥ 12 years of age): One international unit (IU) of IXINITY per kg body weight increases the circulating activity of factor IX by 0.98 IU/dL. - Children (< 12 years of age): One international (IU) of IXINITY per kg body weight increases the circulating activity of factor IX by 0.79 IU/dL.

	<ul style="list-style-type: none">• Initial dose:<ul style="list-style-type: none">- Required factor IX units (IU) = body weight (kg) x desired factor IX increase (% of normal or IU/dL) x reciprocal of observed recovery (IU/kg per IU/dL).- The maintenance dose depends on the type of bleed or surgery, the intensity of the hemostatic challenge, and number of days until adequate wound healing is achieved.• Routine prophylaxis:<ul style="list-style-type: none">- Adolescents/Adults (≥ 12 years of age): 40 to 70 IU/kg twice weekly.- Children (< 12 years of age): 35 to 75 IU/kg twice weekly.
<p>Indication(s) and Intended Population(s)</p>	<p>IXINITY, Coagulation Factor IX (Recombinant), is a human blood coagulation factor indicated in adults and children with hemophilia B for:</p> <ul style="list-style-type: none">• On-demand treatment and control of bleeding episodes• Perioperative management• Routine prophylaxis to reduce the frequency of bleeding episodes

Table of Contents

List of Tables iv

Glossary 5

1. Executive Summary 6

2. Clinical and Regulatory Background 6

 2.1 Disease or Health-Related Condition(s) Studied 6

 2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the
 Proposed Indication(s) 7

 2.4 Previous Human Experience with the Product (Including Foreign Experience)..... 7

 2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission 7

3. Submission Quality and Good Clinical Practices 7

 3.1 Submission Quality and Completeness..... 7

 3.2 Compliance With Good Clinical Practices And Data Integrity..... 7

5. Sources of Clinical Data and Other Information Considered in the Review 7

 5.1 Review Strategy 8

 5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review..... 8

 5.3 Table of Studies/Clinical Trials 8

6. Discussion of Individual Studies/Clinical Trials 10

 6.1 Study APVO101-903 10

 6.1.1 Objectives..... 10

 6.1.2 Design Overview..... 10

 6.1.3 Population 10

 6.1.4 Study Treatments or Agents Mandated by the Protocol 11

 6.1.6 Sites and Centers 12

 6.1.7 Surveillance/Monitoring..... 12

 6.1.8 Endpoints and Criteria for Study Success 12

 6.1.9 Statistical Considerations & Statistical Analysis Plan 12

 6.1.10 Study Population and Disposition 14

 6.1.11 Efficacy Analyses..... 17

 6.1.12 Safety Analyses..... 22

10. Conclusions 24

 10.1 Statistical Issues and Collective Evidence 24

 10.2 Conclusions and Recommendations..... 25

LIST OF TABLES

Table 1 Summary of APVO101-903	9
Table 2 Study Intervention Administered.....	11
Table 3 Demographic and Baseline Characteristics – Safety Population.....	15
Table 4 Bleeding Episodes History – Safety Population.....	16
Table 5 Summary of Annualized Bleeding Rate While on Prophylaxis to Prevent Bleeding Episodes – Safety Population	18
Table 6 Summary of Spontaneous Annualized Bleeding Rate While on Prophylaxis to Prevent Bleeding Episodes – Safety Population.....	19
Table 7 Summary of Bleeding Episode Level Efficacy Endpoints (Overall) – Safety Population	21
Table 8 Treatment Exposure – Safety Population	23
Table 9 Overview of Adverse Events – Safety Population.....	23

GLOSSARY

ABR	annualized bleeding rate
AE	adverse event
Anti-CHOP	antibodies to Chinese hamster ovary cell proteins
ATC	anatomical therapeutic chemical
AUC _{0-t}	area under the plasma concentration curve from time 0 to t
AUC _{0-∞}	area under the plasma concentration curve from time 0 to infinity
BLA	biologics license application
BMI	body mass index
BIMO	Bioresearch and Monitoring
bp	base pair
CHOP	Chinese hamster ovary cell proteins
CI	confidence interval
CL	clearance
C _{max}	maximum post-infusion plasma concentration
CRF	case report form
CSR	clinical study report
DSMB	data and safety monitoring board
ED	exposure days
FDA	Food and Drug Administration
FIX	factor IX
IMP	investigational medicinal product
IU	international units
IV	intravenous
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
MRT	mean residence time
NA	not applicable
PK	pharmacokinetics
PTP	previously treated patient
rFIX	recombinant factor IX
SABR	spontaneous annualized bleeding rate
SAE	serious adverse event
SAP	statistical analysis plan
SMC	Safety Monitoring Committee
SD	standard deviation
TEAE	treatment-emergent adverse event
US	United States
WHO-DD	World Health Organization Drug Dictionary

1. Executive Summary

APVO101 is licensed in the United States (US) as IXINITY for control and prevention of bleeding episodes, and for perioperative management in patients aged ≥ 12 years old with hemophilia B. To fulfill the Pediatrics Research Equity Act (PREA) post-marketing requirement for IXINITY, the applicant completed a clinical study (Study APVO101-903) in pediatric (< 12 years old) previously treated patients (PTPs). Subsequently, the applicant submitted this supplement biologics license application (sBLA) and proposed to expand the labeling indication to include pediatric patients 0 to 12 years of age, with supporting evidence from Study APVO101-903.

Study APVO101-903 was a Phase 3/4, single-arm, open-label study. The purpose of the study was to evaluate the safety, efficacy, and pharmacokinetics (PK) of APVO101 prophylaxis in subjects < 12 years old with severe or moderately severe hemophilia B. The study was designed to gather information in 2 age groups of previously treated (with a minimum of 50 previous exposure days [EDs] to factor IX replacement therapy) pediatric subjects, specifically those < 6 years old and 6 to < 12 years old.

The primary efficacy endpoint of Study APVO101-903 was the annualized bleeding rate (ABR) while on prophylaxis to prevent bleeding episodes. A total of 21 subjects were enrolled in the study and included in the efficacy analysis. The overall mean annualized bleeding rate (ABR) was 2.34 with a 95% confidence interval (CI) of (1.8, 3.1). The overall mean spontaneous annualized bleeding rate (sABRs) was 0.63 with a 95% CI of (0.4, 1.1).

The secondary endpoints included the efficacy ratings in treating bleeds. Overall, 52 bleeding episodes occurred among all 21 subjects. Of the bleeding episodes that required treatment, subjects rated APVO101 efficacy as excellent for 28 episodes (53.8%) and as good for 13 episodes (25.0%). No infusions were required for 9 episodes (17.3%). The mean number of infusions required to treat the bleeding episode was 1.3.

For safety, there were no deaths in the study. Sixteen subjects were reported to have at least 1 TEAE. Two subjects had serious TEAEs; one subject had a TEAE that was assessed as possibly related to the study drug; and two subjects had TEAEs that led to study termination.

Overall, there were no major statistical issues identified during the review of this BLA. Primary results were confirmed by the reviewer's independent analyses. The efficacy results of Study APVO101-903 provide adequate statistical evidence for the proposed indication.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia B (Christmas disease) is a rare hereditary blood disorder caused by deficiency or dysfunction of factor IX (FIX) resulting in bleeding secondary to abnormal

clot formation. Hemophilia B occurs in approximately 1 in 50,000 people and constitutes 20% of the total hemophilia A and B population. The disease presents virtually exclusively in males but is also an X-linked recessive inherited trait carried by women heterozygous for the gene. Spontaneous mutations occur in one-third to one-half of cases, more commonly in severe cases. Children present after circumcision, intramuscular immunization, trauma, or with intracranial hemorrhage. Long-term consequences include hemophilic arthropathy, a potentially devastating complication which can lead to disability or joint replacement.

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

Treatments for hemophilia B require replacement with FIX. FIX formulations include human plasma products such as fresh-frozen plasma or prothrombin complex concentrates. FIX products, either plasma derived or recombinant, are commercially available. Recombinant factor IX (rFIX) preparations are now available and are the mainstay of therapy. Bypassing agents are available in the instance of inhibitor formation but these are not first-line therapy. For details of other treatments, please refer to the clinical review.

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

The investigation medicinal product (IMP) in Study APVO101-903 was IXINITY (recombinant coagulation factor IX). Originally approved by the U.S. FDA in 2014, IXINITY is indicated for the control and prevention of bleeding episodes, and for perioperative management in patients with hemophilia B.

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

Please refer to the clinical 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.

3.2 Compliance With Good Clinical Practices And Data Integrity

Please refer to the clinical and bioresearch and monitoring (BIMO) reviews.

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

5.1 Review Strategy

This review focuses on safety and efficacy results in one single-arm open-label Phase 3/4 study (APVO101-903).

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

- STN 125739/0265 Module 1.14 Labeling
- STN 125739/0265 Module 2.5. Clinical Summary
- STN 125739/0265 Module 5.3.3.5. APVO101-903 Clinical Study Report (CSR) and supporting documents and datasets

5.3 Table of Studies/Clinical Trials

Table 1 summarizes Study APVO101-903 in the pediatric clinical development program.

Table 1 Summary of APVO101-903

Objective(s) of the Study	Study Design and Type of Control	Test Product; Dosage Regimen; Route of Administration	Number of Subjects	Diagnosis of Patients	Duration of Treatment	Study Status
<p><u>Primary</u> Evaluate: Safety in pediatric patients for at least 50 exposure days (ED) Prophylaxis efficacy with respect to breakthrough bleeding and control of hemorrhaging PK Immunogenicity</p> <p><u>Exploratory</u> Evaluate markers of thrombogenicity [D-dimer, Thrombin antithrombin III complex TAT) and fragment 1+2 (F1+2)] during the first 24 hours post infusion of APVO101. Evaluate efficacy for perioperative management in pediatric patients with hemophilia B.</p>	<p>Phase ⅓, single arm, open-label study with three defined phases.</p> <p><u>PK Phase:</u> Initial PK evaluation – single dose of APVO101</p> <p><u>Treatment Phase:</u> APVO101 prophylaxis treatment for 50 ED</p> <p><u>Continuation Phase:</u> After completion of Treatment Phase, subjects may continue APVO101 prophylaxis treatment for an additional ≥ 50 ED</p>	<p>APVO101 (IXINITY), lyophilized coagulation factor IX (recombinant) <u>PK phase:</u> 75 ± 5 IU/kg <u>Treatment Phase/Continuation Phase:</u> 35-75 ± 5 IU/kg twice weekly or as prescribed by investigator. <u>Bleeding Episodes:</u> Minor or moderate: 40 – 60 IU/kg Major or life- threatening: 60 – 100 IU/kg <u>Surgery:</u> If Bolus: Up to 120 IU/kg within 1 hour prior to start, 60 IU/kg 12 hours after the first infusion, up to 120 IU/ kg 24 hours after the first infusion. Continue bolus infusions every 12 hours for a minimum of 3 days post- procedure for major or a minimum of 1 day for minor surgery. Or Continuous Infusion: Target plasma level between 70-100% minimum of 3 days post-procedure for major surgery or a minimum of 1 day for minor surgery.</p> <p>Intravenous</p>	15-22	Hemophilia B (pediatric patients < 11.5 years of age at first dose)	≥ 50 ED	Completed

Source: Table 1 in 2.7.6 Synopses of Individual Studies

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study APVO101-903

Study APVO101-903 (Evaluation of a Recombinant Factor IX Product, APVO101, in Previously-Treated Pediatric Patients with Hemophilia B) is the sole Phase 3/4 trial forming the efficacy database for this BLA.

6.1.1 Objectives

The primary objectives of APVO101-903 were as follows:

- To evaluate safety of APVO101 in pediatric research participants with hemophilia B for at least 50 exposure days (ED)
- To assess efficacy of APVO101 prophylaxis with respect to prevention of breakthrough bleeding and with respect to control of hemorrhaging in pediatric research participants with hemophilia B for at least 50 ED
- To evaluate pharmacokinetics (PK) of APVO101 in pediatric research participants with hemophilia B
- To evaluate APVO101 immunogenicity (development of inhibitory and non-inhibitory factor IX binding antibodies and antibodies to Chinese Hamster Ovary cell proteins [CHOP])

6.1.2 Design Overview

Study APVO101-903 was a Phase 3/4, single-arm, open-label clinical study. The purpose of the study was to evaluate the safety, efficacy, and PK of APVO101 prophylaxis in subjects <12 years old with severe or moderately severe hemophilia B. The study was designed to gather information in 2 age groups of previously treated (with a minimum of 50 previous ED to factor IX replacement therapy) pediatric subjects, specifically those <6 years old and 6 to 12 years old. Study APVO101-903 consisted of 3 distinct phases:

- PK Phase – PK evaluation consisted of administration of a single 75 ± 5 IU/kg dose, followed by factor IX activity and safety assessments up to 50 hours post-infusion.
- Treatment Phase – research participants received APVO101 prophylaxis (starting prophylaxis dose to be determined based on APVO101 recovery; ideally within the recommended dose range: 35 – 75 IU/kg; twice weekly) for 50 EDs (approximately 6 months).
- Continuation Phase – research participants may continue to receive APVO101 prophylaxis (recommended dose range: 35 – 75 IU/kg; twice weekly) for an additional ≥ 50 ED.

6.1.3 Population

Enrolled in this study were previously treated patients (PTP) subjects diagnosed with hemophilia B and aged <11.5 years at the time of first dose and <12 years throughout the

Treatment Phase. PTP were defined as patients who were exposed to a factor IX containing product for ≥ 50 exposure days (EDs). All subjects had severe to moderately severe (factor $\leq 2\%$).

6.1.4 Study Treatments or Agents Mandated by the Protocol

APVO101 is a lyophilized coagulation factor IX (recombinant) for IV administration. The dose, schedule and route of administration of the investigational product are summarized in Table 2.

Table 2 Study Intervention Administered

Phase	Regimen	Strength
Treatment Phase	Prophylaxis	Single IV 35-75 IU/kg dose of APVO101 twice weekly or at a frequency determined as appropriate by the Investigator
	Minor/moderate bleeding episodes	APVO101 IV 40-60 IU/kg (single dose)
	Major/life-threatening bleeding episodes	APVO101 IV 60-100 IU/kg (single dose)
Continuation Phase	Prophylaxis	Single IV 35-75 IU/kg of APVO101 twice weekly or at a frequency determined as appropriate by the Investigator
	Minor/moderate bleeding episodes	APVO101 IV 40-60 IU/kg (single dose)
	Major/life-threatening bleeding episodes	APVO101 IV 60-100 IU/kg (single dose)
Surgery	Bolus	Up to 120 IU/kg APVO101 IV within 1 hour before the procedure; followed by ~60 IU/kg at 12 hours and up to 120 IU/kg at 24 hours after the first infusion. Continue bolus infusions q12h as necessary based on minor or major surgical procedure.
	Continuous	Dose based on plasma level maintained between 70% and 110%. Continue for minimum 1 day for minor procedure and 3 days for major procedure.

Source: Table 5 in APVO101-903 Clinical Study Report

6.1.6 Sites and Centers

This was a multicenter study conducted at 10 sites in 6 countries: Brazil, Georgia, Moldova, South Africa, Turkey, and Ukraine.

6.1.7 Surveillance/Monitoring

Please refer to the clinical review.

6.1.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint was annualized bleeding rate (ABR).

The following secondary efficacy endpoints were evaluated at the bleeding episode level:

- Subject rating of efficacy.
- Change in pain.
- Change in swelling.
- Time from onset of bleeding to the first infusion.
- Time from onset of treatment until resolution of the bleeding episode.
- Number of infusions required to treat the bleeding episode.

The following secondary efficacy endpoints were evaluated at the subject level:

- Investigator rating of APVO101 prophylaxis efficacy.
- Investigator rating of APVO101 efficacy for control and management of bleeding episodes.

The safety endpoints were as follows:

- Adverse events (AE).
- Inhibitory factor IX antibodies.
- Non-inhibitory factor IX antibodies.
- Anti-Chinese hamster ovary cell protein (CHOP) antibodies.
- Thrombogenic markers.

The immunogenicity endpoints were:

- Inhibitory factor IX antibodies.
- Non-inhibitory factor IX antibodies.
- Anti-CHOP antibodies.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size

No formal sample size calculation was performed given that all planned analyses are descriptive in nature. Up to 22 subjects were planned to be enrolled to ensure that at least 15 to 20 evaluable subjects complete the study (i.e., completion of PK assessments and a minimum of 50 ED).

Definitions of analysis populations

- Screened population: All screened subjects.
- Safety population: All subjects who received at least one dose of the study drug. This population was to be used for all safety and efficacy analyses.

Statistical Analysis for Primary Efficacy Endpoint

The primary analysis of the primary endpoint was to analyze the annualized bleeding rates (ABR) while on prophylaxis to prevent bleeding episodes. The ABR was defined as the number of bleeding episodes per year. ABR was calculated for the Treatment Phase, for the Continuation Phase, and overall. The estimated 95% CIs were computed based on the assumption that ABRs followed a Poisson distribution.

ABR overall is based on time period from first dose after PK Phase up to 3 days after the last dose of APVO101 given for prophylaxis or the date of end of study, whichever was earlier.

ABR Treatment Phase started from first dose after PK Phase up to 3 days after the last dose of APVO101 given for prophylaxis up to 50 ED, or the date of end of study, whichever was earlier.

ABR Continuation Phase started from first dose after 50 ED up to 3 days after last dose of APVO101 given for prophylaxis or the date of end of study, whichever was earlier.

In addition, analysis of ABR was to be repeated on the normalized data (square-root transformation will be used to normalize ABR).

Number of subjects with at least one bleeding episode and no bleeding episodes was also to be summarized.

The analysis of ABR was to be repeated for Spontaneous ABR which will consider only spontaneous bleeding episodes in the numerator. Denominator was to remain the same as for ABR. Spontaneous ABR for Treatment, Continuation phases as well as overall were to be derived.

Statistical Analysis for Secondary Efficacy Endpoint

Both types of secondary efficacy endpoints (bleeding episode level and subject level) were to be presented descriptively for the Treatment Phase, Continuation Phase and overall (all bleeding episodes and subject level assessments in a subject).

Statistical Analysis for Safety Endpoint

Safety was to be evaluated by presenting summaries of exposure to study treatment, AEs, physical examination, vital signs, local laboratory evaluations (hematology, serum chemistry, and urinalysis) and central laboratory evaluations (inhibitory factor IX antibodies, non-inhibitory factor IX binding antibodies, anti-CHOP antibodies, and thrombogenic markers).

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 21 subjects were enrolled in the study and included in the Safety population. There were 10 subjects in the <6 years group and 11 subjects in the 6 to <12 years group.

6.1.10.1.1 Demographics

Overall, the mean age of the subjects was 6.2 years. All subjects were male. Most subjects were White (n=18, 85.7%), followed by Black or African American (n=3, 14.3%). Two subjects (9.5%) were Hispanic or Latino. Descriptive statistics for demographic and baseline characteristics are summarized by age group for subjects in the Safety Population in Table 3.

Table 3 Demographic and Baseline Characteristics – Safety Population

Parameter	Age Group: < 6 years (N = 10) n (%)	Age Group: 6 to < 12 years (N = 11) n (%)	Total (N = 21) n (%)
Age (years) [1], n	10	11	21
Mean	3.3	8.7	6.2
SD	1.36	1.00	2.99
Median (Q1-Q3)	3.4 (2.2-4.1)	8.6 (8.0-9.7)	7.2 (3.7-8.6)
Min, Max	1, 5	7, 10	1, 10
Race, n (%)			
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Black or African American	2 (20.0)	1 (9.1)	3 (14.3)
Asian	0 (0.0)	0 (0.0)	0 (0.0)
White	8 (80.0)	10 (90.9)	18 (85.7)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, n (%)			
Hispanic or Latino	1 (10.0)	1 (9.1)	2 (9.5)
Not Hispanic or Latino	9 (90.0)	10 (90.9)	19 (90.5)
Gender, n (%)			
Male	10 (100)	11 (100)	21 (100)
Female	0 (0.0)	0 (0.0)	0 (0.0)
Weight (kg), n	10	11	21
Mean	16.01	35.48	26.21
SD	3.535	8.444	11.856
Median (Q1-Q3)	16.65 (12.90-17.50)	36.10 (26.20-40.80)	25.30 (16.80-36.10)
Min, Max	11.6, 23.0	25.3, 49.5	11.6, 49.5
Height (cm), n	10	11	21
Mean	98.85	137.00	118.83
SD	13.671	6.946	22.123
Median (Q1-Q3)	103.50 (91.00-108.00)	138.00 (130.50-141.00)	126.00(105.00-138.00)
Min, Max	75.0, 120.0	126.0, 148.0	75.0, 148.0
BMI (kg/m2), n	10	11	21
Mean	16.43	18.78	17.66
SD	1.988	3.732	3.192
Median (Q1-Q3)	15.75(15.00-17.05)	17.71 (16.02-21.43)	16.30 (15.27-19.19)
Min, Max	14.7, 20.6	15.1, 25.7	14.7, 25.7

Source: Table 11 in APVO101-903 Clinical Study Report

N = Number of subjects in population; n (%) = Count and percentage.

Note: [1] Age at informed consent. Subjects in the younger age group must remain <6 years age throughout the treatment period (at least 50 ED) and the upper age group must remain <12 years throughout the treatment period (at least 50 ED). Percentages are based on N.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Hemophilia B History

The mean age at diagnosis of hemophilia B was 0.7 years and the mean time since the diagnosis was 59.76 months. Thirteen (61.9%) subjects had severe disease, defined as factor IX activity <1%. Eight (38.1%) subjects had moderately severe disease, defined as

factor IX activity 1% to <2%. At study entry, the type of factor IX mutation was unknown in 19 (90.5%) subjects and known in 2 (9.5%) subjects. The factor IX mutation was nonsense in 1 (4.8%) subject and frameshift (4.8%) in 1 subject. The mean time from the first treated bleeding episode was 58.19 months and the mean total number of factor IX replacement therapy in ED was 221.67. The right knee (n=2) was the only affected target joint. Symptoms included swelling, loss of range of motion, and flexion.

Bleeding Episodes History

Subject bleeding episodes history are summarized in Table 4. Overall, the mean number of bleeding episodes in the 6 months before screening was 3.5 (median 2.0) and the mean percent of spontaneous bleeding episodes was 29.6% (median 0.0). The most commonly administered number of administrations required to control bleeding episodes was 2-3 (8 subjects [38.1%]).

Table 4 Bleeding Episodes History – Safety Population

Parameter	Age Group: < 6 years (N = 10) n (%)	Age Group: 6 to < 12 years (N = 11) n (%)	Total (N = 21) n (%)
Number of bleeding episodes during 6 months prior to screening, n	10	11	21
Mean	3.0	3.9	3.5
SD	4.97	3.59	4.21
Median (Q1-Q3)	1.0 (0.0-4.0)	4.0 (0.0-6.0)	2.0 (0.0-4.0)
Min, Max	0, 16	0, 12	0, 16
Percentage of spontaneous bleeding episodes (%), n	10	11	21
Mean	18.3	39.8	29.6
SD	33.73	39.97	37.84
Median (Q1-Q3)	0.0 (0.0-33.0)	30.0 (0.0-83.0)	0.0 (0.0-50.0)
Min, Max	0, 100	0, 100	0, 100
Number of infusions needed to control the bleeding episode			
0	3 (30.0)	3 (27.3)	6 (28.6)
1	2 (20.0)	3 (27.3)	5 (23.8)
2-3	5 (50.0)	3 (27.3)	8 (38.1)
4-5	0 (0.0)	1 (9.1)	1 (4.8)
6+	0 (0.0)	1 (9.1)	1 (4.8)

Source: Table 14 in APVO101-903 Clinical Study Report

N = Number of subjects in population. If bleeding history for a patient is not documented, estimation is provided on CRF. Documented bleeding history data and their estimation (for patients who do not have bleeding history documented) are summarized together in the table.

6.1.10.1.3 Subject Disposition

Among the 21 subjects enrolled in the study, 19 subjects completed 50 ED visits and proceeded to the Continuation Phase. Two subjects discontinued from the Treatment Phase: 1 subject due to an adverse event and 1 subject due to voluntary withdrawal by the

subject or parent/legal guardian. Of 19 subjects who entered the Continuation Phase, 4 subjects had >50 ED visits but <100 ED visits; 15 subjects had \geq 100 ED visits. Fourteen subjects completed the Continuation Phase. Of the 5 subjects who discontinued, 1 was due to non-compliance; 1 was due to an adverse event; and 3 were due to other reasons.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The ABRs while on prophylaxis to prevent bleeding episodes for treatment phase, continuation phase, and overall are summarized in Table 5.

Table 5 Summary of Annualized Bleeding Rate While on Prophylaxis to Prevent Bleeding Episodes – Safety Population

Period	Parameter	Age Group: < 6 years (N = 10) n (%)	Age Group: 6 to < 12 years (N = 11) n (%)	Total (N = 21) n (%)
Treatment phase	Number of subjects with no bleeding episodes	4 (40.0)	6 (54.5)	10 (47.6)
	Actual ABR, n	10	11	21
	Mean	4.44	1.56	2.93
	SD	6.149	1.950	4.592
	Median (Q1-Q3)	1.71 (0.00-6.52)	0.00 (0.00-4.17)	1.12 (0.00-4.35)
	Min, Max	0.0, 18.7	0.0, 4.4	0.0, 18.7
	Estimated ABR 95% CI [1]	4.44 [3.3;6.0]	1.56 [1.0;2.5]	2.93 [2.3;3.8]
Continuation phase	Number of subjects with no bleeding episodes	5 (50.0)	5 (45.5)	10 (47.6)
	Actual ABR, n	8	11	19
	Mean	1.49	1.06	1.24
	SD	2.354	1.699	1.951
	Median (Q1-Q3)	0.00 (0.00-2.94)	0.54 (0.00-1.62)	0.00 (0.00-1.82)
	Min, Max	0.0, 6.1	0.0, 5.6	0.0, 6.1
	Estimated ABR 95% CI [1]	1.49 [0.8;2.6]	1.06 [0.6;1.9]	1.24 [0.8;1.9]
Overall	Number of subjects with no bleeding episodes	4 (40.0)	3 (27.3)	7 (33.3)
	Actual ABR, n	10	11	21
	Mean	3.60	1.19	2.34
	SD	5.820	1.481	4.226
	Median (Q1-Q3)	1.35 (0.00-5.86)	0.86 (0.00-1.66)	0.86 (0.00-1.96)
	Min, Max	0.0, 18.7	0.0, 5.2	0.0, 18.7
	Estimated ABR 95% CI [1]	3.60 [2.6;5.0]	1.19 [0.7;2.0]	2.34 [1.8;3.1]

Source: Table 18 in APVO101-903 Clinical Study Report

N = Number of subjects in population, Treatment phase = up to 50 ED (including PK Phase), Continuation phase = after 50 ED.

[1] 95% exact confidence interval for the mean, assuming that the rates follow a Poisson distribution (using proc genmod SAS procedure).

Similarly, spontaneous annualized bleeding rates (SABRs) while on prophylaxis to prevent bleeding episodes are summarized in Table 6.

Table 6 Summary of Spontaneous Annualized Bleeding Rate While on Prophylaxis to Prevent Bleeding Episodes – Safety Population

Period	Parameter	Age Group: < 6 years (N = 10) n (%)	Age Group: 6 to < 12 years (N = 11) n (%)	Total (N = 21) n (%)
Treatment phase	Number of subjects with no bleeding episodes	8 (80.0)	8 (72.7)	16 (76.2)
	Actual sABR, n	10	11	21
	Mean	1.06	0.58	0.81
	SD	2.668	0.998	1.939
	Median (Q1-Q3)	0.00 (0.00-0.00)	0.00 (0.00-2.02)	0.00 (0.00-0.00)
	Min, Max	0.0, 8.4	0.0, 2.2	0.0, 8.4
	Estimated SABR 95% CI [1]	1.06 [0.6;1.9]	0.58 [0.3;1.3]	0.81 [0.5;1.3]
Continuation phase	Number of subjects with no bleeding episodes	7 (70.0)	6 (54.5)	10 (61.9)
	Actual sABR, n	8	11	19
	Mean	0.41	0.71	0.58
	SD	1.150	1.332	1.235
	Median (Q1-Q3)	0.00 (0.00-0.00)	0.00 (0.00-1.08)	0.00 (0.00-0.56)
	Min, Max	0.0, 3.3	0.0, 4.5	0.0, 4.5
	Estimated ABR 95% CI [1]	0.41 [0.1;1.2]	0.71 [0.4;1.4]	0.58 [0.3;1.1]
Overall	Number of subjects with no bleeding episodes	8 (80.0)	5 (45.5)	13 (61.9)
	Actual sABR, n	10	11	21
	Mean	0.55	0.70	0.63
	SD	1.476	1.089	1.257
	Median (Q1-Q3)	0.00 (0.00-0.00)	0.44 (0.00-0.91)	0.00 (0.00-0.85)
	Min, Max	0.0, 4.7	0.0, 3.7	0.0, 4.7
	Estimated ABR 95% CI [1]	0.55 [0.2;1.3]	0.70 [0.3;1.4]	0.63 [0.4;1.1]

Source: Table 19 in APVO101-903 Clinical Study Report

Definitions: N = Number of subjects in population, Treatment phase = up to 50 ED (including PK phase), Continuation phase = after 50 ED.

[1] 95% exact confidence interval for the mean, assuming that the rates follow a Poisson distribution (using proc genmod SAS procedure).

6.1.11.2 Analyses of Secondary Endpoints

Secondary Efficacy Endpoint Analysis at the Bleeding Episode Level

Overall efficacy at the bleeding episode level is summarized in Table 7. Fifty-two bleeding episodes occurred overall, 28 in the <6 yr age group and 24 in the 6 to <12 yr age group. Of the bleeding episodes that required treatment, subjects rated APVO101 efficacy as excellent for 28 episodes (53.8%) and as good for 13 episodes (25.0%). No infusions were required for 9 episodes (17.3%). Data were missing for 2 episodes. There was no pain during 22 bleeding episodes (42.3%), very little pain during 11 episodes (21.2%), little pain during 9 episodes (17.3%); moderate pain during 5 episodes (9.6%), moderate to severe pain during 3 episodes (5.8%), and severe pain during 1 episode (1.9%) (data were missing for 1 episode). The pain stopped in <2 hours in 9 episodes (17.3%); in ≥ 2 hours but <6 hours in 8 episodes (15.4%); in ≥ 12 hours but <24 hours in 2 episodes (3.8%); in ≥ 24 hours but <48 hours in 3 episodes (5.8%); and in ≥ 48 hours but <72 hours in 1 episode (1.9%) (data for 1 episode were missing).

No swelling occurred in 25 bleeding episodes. Among the 26 episodes with swelling, the swelling subsided in <2 hours in 4 episodes (7.7%); in ≥ 2 hours but <6 hours in 4 episodes (7.7%); in ≥ 6 hours but <12 hours in 6 episodes (11.5%); in ≥ 12 hours but <24 hours in 2 episodes (3.8%); in ≥ 24 hours but <48 hours in 4 episodes (7.7%); ≥ 48 hours but <72 hours in 1 episode (1.9%); and ≥ 72 hours in 5 episodes (9.6%). In addition, data were missing for 1 episode.

The mean time from the onset of bleeding to administration of the first infusion was 216.5 minutes (34 episodes). The mean time from onset of treatment until resolution of bleeding was 1220.1 minutes (33 episodes). The mean number of infusions required to treat the bleeding episode was 1.3.

Table 7 Summary of Bleeding Episode Level Efficacy Endpoints (Overall) – Safety Population

Parameter	Age Group: < 6 years (N = 10)	Age Group: 6 to < 12 years (N = 11)	Total (N = 21)
Number of bleeding episodes, N1	28	24	52
Subject's rating of efficacy, n (%)			
Excellent	15 (53.6)	13 (54.2)	28 (41.7)
Good	6 (21.4)	7 (29.2)	13 (25.0)
Fair	0 (0.0)	0 (0.0)	0 (0.0)
Poor	0 (0.0)	0 (0.0)	0 (0.0)
No infusions were required to treat the bleeding episode	7 (25.0)	2 (8.3)	9 (17.3)
Missing [3] [4]	0 (0.0)	2 (8.3)	2 (3.8)
Time needed for pain to stop, n (%)			
There was no pain	18 (64.3)	10 (41.7)	28 (53.8)
Less than 2 hours	6 (21.4)	3 (12.5)	9 (17.3)
2 or more hours, but less than 6	3 (10.7)	5 (20.8)	8 (15.4)
6 or more hours, but less than 12	0 (0.0)	0 (0.0)	0 (0.0)
12 or more hours, but less than 24	0 (0.0)	2 (8.3)	2 (3.8)
24 or more hours, but less than 48	1 (3.6)	2 (8.3)	3 (5.8)
48 or more hours, but less than 72	0 (0.0)	1 (4.2)	1 (1.9)
72 or more hours	0 (0.0)	0 (0.0)	0 (0.0)
Missing [3]	0 (0.0)	1 (4.2)	1 (1.9)
Highest level of pain experienced during the episode, n (%)			
No pain	15 (53.6)	7 (29.2)	22 (42.3)
Very little pain	5 (17.9)	6 (25.0)	11 (21.2)
Little pain	4 (14.3)	5 (20.8)	9 (17.3)
Moderate pain	4 (14.3)	1 (4.2)	5 (9.6)
Moderate to severe pain	0 (0.0)	3 (12.5)	3 (5.8)
Severe pain	0 (0.0)	1 (4.2)	1 (1.9)
Missing [3]	0 (0.0)	1 (4.2)	1 (1.9)
Time needed for swelling to go down, n (%)			
No swelling present	15 (53.6)	10 (41.7)	25 (48.1)
Less than 2 hours	2 (7.1)	2 (8.3)	4 (7.7)
2 or more hours, but less than 6	3 (10.7)	1 (4.2)	4 (7.7)
6 or more hours, but less than 12	3 (10.7)	3 (12.5)	6 (11.5)
12 or more hours, but less than 24	1 (3.6)	1 (4.2)	2 (3.8)
24 or more hours, but less than 48	1 (3.6)	3 (12.5)	4 (7.7)
48 or more hours, but less than 72	0 (0.0)	1 (4.2)	1 (1.9)
72 or more hours	3 (10.7)	2 (8.3)	5 (9.6)
Missing [3]	0 (0.0)	1 (4.2)	1 (1.9)
Time from onset of bleeding to the first infusion (min) [1] [3], n	17	17	34
Mean	172.4	260.6	216.5
SD	260.78	667.90	506.26
Median (Q1-Q3)	30.0 (0.0-255.0)	30.0 (0.0-145.0)	30.0 (0.0-220.0)
Min, Max	0, 951	0, 2740	0, 2740
Time from onset of treatment until resolution of the bleeding	16	17	33

episode (min) [2] [3], n			
Mean	766.5	1647.1	1220.1
SD	1267.45	2123.66	1791.00
Median (Q1-Q3)	105.0 (50.0-1362.0)	240.0 (45.0-3060.0)	120.0 (45.0-1485.0)
Min, Max	-510, 4300	10, 5900	-510, 5900
Number of infusions required to treat the bleeding episode as continuous variable, n			
Mean	1.0	1.5	1.3
SD	0.92	1.22	1.09
Median (Q1-Q3)	1.0 (0.5-1.0)	1.0 (1.0-2.0)	1.0 (1.0-1.0)
Min, Max	0, 4	0, 5	0, 5
Number of infusions required to treat the bleeding episode as categorical variable, n (%) [3]			
0 infusions	7 (25.0)	2 (8.3)	9 (17.3)
1 infusion	16 (57.1)	15 (62.5)	31 (59.6)
2 infusions	3 (10.7)	2 (8.3)	5 (9.6)
3 infusions	1 (3.6)	3 (12.5)	4 (7.7)
4 infusions	1 (3.6)	1 (4.2)	2 (3.8)
5 infusions	0 (0.0)	1 (4.2)	1 (1.9)

Source: Table 22 in APVO101-903 Clinical Study Report

n (%) = Count and percentage; N = Number of subjects in population; N1 = Number of bleeding episodes. Percentages are based on N1.

[1] There were no infusions required for 9 BEs (patient (b) (6) 2 episodes, patient (b) (6) 1 episode, patient (b) (6) 4 episodes, patient (b) (6) 2 episodes) and it is not possible to derive time from bleeding start to first infusion for 8 episodes (patient (b) (6) episodes 3, 6 and 7, patient (b) (6) episode 2, patient (b) (6) episodes 1, 6 and 7, patient (b) (6) episode 8).

[2] There were no infusions required for 9 BEs (patient (b) (6) 2 episodes, patient (b) (6) 1 episode, patient (b) (6) 4 episodes, patient (b) (6) 2 episodes) and it is not possible to derive time from treatment start to end of bleeding for 9 episodes (patient (b) (6) episodes 4, 5, 6 and 7, patient (b) (6) episode 2, (b) (6) episodes 1, 6 and 7, patient (b) (6) episode 8).

[3] Patient (b) (6) is reported to have 1 infusion to control bleeding episode 1 on 'Bleeding Episode' CRF page while no corresponding infusion to treat this bleeding is recorded. The site clarified that the patient received a regular scheduled dose prior to onset of bleeding and no additional treatment was needed.

[4] Site confirmed that efficacy assessment of bleeding episode 1 in patient (b) (6) was not performed.

6.1.11.4 Dropouts and/or Discontinuations

Two subjects discontinued from the Treatment Phase: one subject due to an adverse event and one subject due to voluntary withdrawal by the subject or parent/legal guardian. Five subjects discontinued from the Continuation Phase, one was due to non-compliance; one was due to an adverse event; and three were due to other reasons. Compared to the total number of subjects and their time in the study, I consider the impact of these discontinuations on the analysis results is small.

6.1.12 Safety Analyses

Extent of Exposure

The total mean ED was 158.7 (median 163.0 ED, minimum 13 ED, maximum 256 ED). In the event that a subject received more than 1 infusion in a single day, all infusions on

that day were counted as 1 ED. Nineteen subjects had ≥ 50 ED, 16 subjects had ≥ 100 ED, 12 subjects had ≥ 150 ED, and 7 subjects had ≥ 200 ED (Table 8).

Table 8 Treatment Exposure – Safety Population

Parameter	Age Group: < 6 years (N = 10)	Age Group: 6 to < 12 years (N = 11)	Total (N = 21)
Exposure Days, n	10	11	21
Mean	107.9	204.9	158.7
SD	69.78	51.26	73.76
Median (Q1-Q3)	109.0 (56.0-163.0)	233.0 (163.0-250.0)	163.0 (108.0-233.0)
Min, Max	13, 194	108, 256	13, 256
Subjects with ≥ 50 ED	8 (80.0)	11 (100)	19 (90.5)
Subjects with ≥ 100 ED	5 (50.0)	11 (100)	16 (76.2)
Subjects with ≥ 150 ED	3 (30.0)	9 (81.8)	12 (57.1)
Subjects with ≥ 200 ED	0 (0.0)	7 (63.6)	7 (33.3)

Source: Table 27 in APVO101-903 Clinical Study Report
N = Number of subjects in population; n (%) = Count and percentage.

Adverse Events

Sixteen subjects were reported to have at least one TEAE. Two subjects had serious TEAEs; one subject had a TEAE that was assessed as possibly related to the study drug; and two subjects had TEAEs that led to study termination. There were no deaths in the study (Table 9).

Table 9 Overview of Adverse Events – Safety Population

	Age Group: < 6 years (N = 10) n (%) E	Age Group: 6 to < 12 years (N = 11) n% E	Total (N = 21) n%E
Number of subjects with at least one:			
TEAE [1]	9 (90.0) 27	7 (63.6) 22	16 (76.2) 49
Serious TEAE	0 (0.0) 0	2 (18.2) 2	2 (9.5) 2
Non-serious TEAE	9 (90.0) 27	7 (63.6) 20	16 (76.2) 47
Drug-related TEAE [2]	1 (10.0) 1	0 (0.0) 0	1 (4.8) 1
TEAE leading to study termination	1 (10.0) 1	1 (9.1) 1	2 (9.5) 2
TEAE leading to death	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0

Source: Table 28 in APVO101-903 Clinical Study Report
E = number of events; n (%) = Count and percentage; N = Number of subjects in population. Percentages are based on N.

[1] A TEAE is defined as an adverse event that occurs or worsens after the first study drug administration.

[2] A TEAE is considered drug-related if relationship to study drug is missing, “probably related”, “possibly related” or “definitely related.”

6.1.12.1 Methods

Subjects who experienced TEAEs are presented by MedDRA System Organ Class (SOC) and Preferred Term (PT). The most commonly reported TEAEs were infections: nasopharyngitis, bronchitis, influenza, viral respiratory tract infection, respiratory tract infection, and tonsillitis; and respiratory, thoracic and mediastinal disorders: oropharyngeal pain and rhinorrhoe. Please refer to the clinical review for details.

6.1.12.3 Deaths

There were no deaths among subjects who participated in this study.

6.1.12.4 Nonfatal Serious Adverse Events

Two subjects experienced SAEs during their participation in the study: one developed severe haematuria, the other experienced moderate spinal compression fracture. The Investigator assessed these SAEs as unrelated to the study drug.

6.1.12.5 Adverse Events of Special Interest (AESI)

Three of 21 subjects developed anti-CHOP antibodies. In 1 subject, the anti-CHOP protein response was persistent, 1 subject tested positive at the 50th ED and End of Study visit, and 1 subject tested positive at the End of Study visit. There were no safety or efficacy concerns with these subjects. Three of 21 subjects tested positive for non-inhibitory factor IX antibodies. No inhibitory factor IX antibodies were seen in the study subjects.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

APVO101 is a human blood coagulation factor licensed in the United States (US) as IXINITY® for control and prevention of bleeding episodes, and for perioperative management in adults and children with hemophilia B.

Study APVO101-903 was a Phase 3/4, single-arm, open-label study to evaluate the safety, efficacy, and pharmacokinetics (PK) of IXINITY prophylaxis in subjects <12 years old with severe or moderately severe hemophilia B. The study included a 50-hour PK Phase, a Treatment Phase of approximately 6 months, and a Continuation Phase for ≥6 months. Twenty-one subjects were enrolled in the study with 10 in the <6 years group and 11 in the 6 to <12 years group. Nineteen subjects completed the Treatment Phase and proceeded to the Continuation Phase, and fourteen subjects completed the Continuation Phase.

The primary efficacy endpoint analysis yielded an overall mean annualized bleeding rate (ABR) of 2.34 with a 95% confidence interval (CI) of (1.8, 3.1). The overall mean spontaneous annualized bleeding rates (sABRs) was 0.63 with a 95% confidence interval (CI) of (0.4, 1.1).

The secondary endpoints included the efficacy ratings in treating bleeds. Overall, fifty-two bleeding episodes occurred among all 21 subjects. No infusions were required for 9 episodes (17.3%). Of the bleeding episodes that required treatment, subjects rated APVO101 efficacy as excellent for 28 episodes (53.8%) and as good for 13 episodes (25.0%). The mean number of infusions required to treat the bleeding episode was 1.3.

For safety evaluation, there were no deaths in the study. Sixteen subjects were reported to have at least 1 TEAE, and two subjects had serious TEAEs. One subject had a TEAE that

was assessed as possibly related to the study drug. Two subjects had TEAEs that led to study termination.

10.2 Conclusions and Recommendations

In conclusion, there were no major statistical issues related to the submission. Primary results were confirmed by the reviewer's independent analyses. The efficacy results of Study APVO101-903 provide adequate statistical evidence for the proposed indication.