

BLA Clinical Review Memorandum

Application Type	BLA Efficacy Supplement
STN	125426/223
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Division / Office	DH/OBRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Christine Knoll, MD
Review Completion Date / Stamped Date	March 22, 2024
Supervisory Concurrence	Lola Fashoyin-Aje, MD, MPH
Applicant	Medexus Pharma, Inc
Established Name	Coagulation FIX (Recombinant) APVO101
(Proposed) Trade Name	Ixinity
Pharmacologic Class	Coagulation Factor
Formulation(s), including Adjuvants, etc.	Intravenous Injection
Dosage Form(s) and Route(s) of Administration	Lyophilized powder for injection
Dosing Regimen	250, 500, 1000, 1500, 2000, or 3000 IU/vial
Indication(s) and Intended Population(s)	Control and prevention of bleeding episodes and perioperative management in subjects with Hemophilia B < 12 years
Orphan Designated (Yes/No)	No

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GLOSSARY

ABR	annualized bleeding rate
AE	adverse event
Anti-CHOPP	anti-Chinese hamster ovary cell proteins
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
CBC	complete blood count
CHOPP	Chinese hamster ovary
CL	clearance
C _{max}	maximum post-infusion plasma concentration
CMC	chemistry, manufacturing, and controls
ED	exposure day
F1+2	prothrombin fragment 1+2
FDA	Food and Drug Administration
FIX	Factor IX
IND	Investigational New Drug
PeRC	Pediatric Review Committee
PI	package insert
PK	pharmacokinetics
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PTP	previously treated subject
sBLA	supplemental Biologics License Application
SMC	Safety Monitoring Committee
TAT	thrombin-antithrombin III complex
TEAE	treatment-emergent adverse event

1. EXECUTIVE SUMMARY

Ixinity (APVO101) is a recombinant human coagulation Factor IX (FIX) that is secreted by genetically engineered mammalian cells derived from a Chinese hamster ovary (CHOPP) cell line. Ixinity is a lyophilized preparation administered as intravenous replacement therapy for the control and prevention of bleeding episodes, routine prophylaxis, and perioperative management in subjects ≥ 12 years of age with hemophilia B. Ixinity was originally approved April 29, 2015, for the control and prevention of bleeding episodes and perioperative management in subjects ≥ 12 years of age with hemophilia B. The indication was expanded on September 25, 2020, to include routine prophylaxis to reduce the frequency of bleeding episodes in adults and adolescents ≥ 12 years of age with hemophilia B; this approval was subsequently rescinded for adolescents (12 to 17 years of age) on February 17, 2021, and reinstated on November 7, 2022.

Medexus Pharmaceuticals, Inc., submitted the current efficacy supplemental Biologics License Application (sBLA), seeking a label expansion to include control and prevention of bleeding episodes, routine prophylaxis, and perioperative management in children < 12 years of age with hemophilia B. The sBLA contains data from APVO101-903 (NCT03855280), a single phase 3/4 prospective, single-arm, open-label, uncontrolled, multicenter study evaluating the safety, efficacy, and pharmacokinetics (PK) of Ixinity prophylaxis in previously treated subjects (PTPs) < 12 years of age with severe or moderately severe hemophilia. The study enrolled subjects into two cohorts: < 6 years of age and 6 to < 12 years of age. The study consisted of three phases: (PK phase, treatment phase, and continuation phase), as described below:

- PK Phase: There was a screening period (21 to 5 days before the PK phase) followed by a three-to-four-day washout period for subjects on standard half-life FIX product or three half-lives washout period for subjects on an extended half-life FIX product.
- Treatment phase: The subjects were dosed with 35 to 75 IU/kg once to twice weekly. The treatment phase duration per subject was approximately 6 months or 50 exposure days (EDs).
- Continuation phase: Subjects continued prophylaxis into the continuation phase for at least an additional 6 months or 50 ED. They were continued on their last dose of prophylaxis during the treatment phase.

The primary efficacy endpoint was annualized bleeding rate (ABR) while on prophylactic treatment with Ixinity. ABR was calculated for the treatment phase, continuation phase, and overall, for all subjects. Spontaneous ABR was also calculated for the treatment phase, for the continuation phase, and overall, for all subjects. ABR was defined as the number of bleeding episodes per year. Spontaneous ABR was defined as the number of spontaneous bleeding episodes per year. The ABR was compared with ABR in subjects 6 months prior to screening.

The primary safety endpoints were adverse events (AEs), inhibitory FIX antibodies, non-inhibitory FIX antibodies, anti-Chinese hamster ovary cell protein (CHOPP) antibodies, and thrombogenic markers. Immunogenicity endpoints included inhibitory FIX antibodies, non-inhibitory FIX antibodies, and anti-CHOPP antibodies.

The PK endpoints included maximum post-infusion plasma concentration (C_{max}), incremental recovery, in vivo recovery, area under the plasma concentration curve from time 0 to infinity ($AUC_{0-\infty}$), area under the plasma concentration curve from time 0 to t (AUC_{0-t}), mean residence time, elimination rate constant, terminal half-life.

The secondary efficacy endpoints included assessment of Ixinity treatment at the bleeding episodes level and the subject level. At the bleeding episode level, the endpoints included measures reported by the subject maintained in the subject diary for each bleeding episode including 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, and number of infusions required to treat the bleeding episode. Subjects then rated the efficacy of Ixinity for each bleeding episode based on a four-point scale that included the defined ratings of excellent, good, fair, and poor. At the subject level, the endpoints included investigator rating of Ixinity prophylaxis efficacy and investigator rating of Ixinity efficacy for control and management of bleeding episodes.

The exploratory efficacy endpoint was perioperative management with Ixinity including surgeon assessment of estimated blood loss at the time of surgery and surgeon assessment of post-surgery blood loss (at 12- and 24-hour post-surgery timepoints).

The exploratory safety endpoints included the thrombogenicity endpoints D-dimer, thrombin-antithrombin III complex (TAT), and fragment 1+2 (F1+2). These were evaluated during the first 24 hours post-infusion of Ixinity.

Results – APVO101-903

Subject Disposition

PK phase: A total of 21 subjects were enrolled in the PK phase; however, only 20 subjects were included in the PK analysis during the PK phase at a dose of 75 IU/kg. One subject was excluded from PK analysis due to incorrect dosing for the PK studies.

Treatment phase: A total of 21 subjects enrolled in the treatment phase. There were 2 cohorts with 10 subjects <6 years of age and 11 subjects 6 to <12 years of age. All 21 subjects were used for analysis of safety and efficacy in the treatment phase. Four subjects received once-weekly dosing in the younger cohort.

Continuation phase: A total of 19 subjects completed 50 EDs during the treatment phase and proceeded to the continuation phase. Of these 19 subjects, four had >50 EDs but <100 EDs, 15 had \geq 100 EDs, and 14 completed the continuation phase.

Efficacy Results

For the primary endpoint, the mean ABR was 2.93 in the treatment phase, 1.24 in the continuation phase, and 2.34 overall. The historical mean ABR 6 months prior to enrollment was 3.5. The efficacy analyses included all 21 subjects enrolled.

Fifty-two bleeding episodes occurred overall (treatment and continuation phase), 28 in the age group <6 years of age and 24 in those 6 to <12 years of age. Of the bleeding episodes that required treatment, subjects rated efficacy as excellent for 28 episodes (53.8%) and as good for 13 episodes (25.0%). Average number of infusions to treat bleeding episodes was 1.3. In 45 of 52 (86.5%) episodes, hemostasis was achieved with zero to two infusions. For four bleeding episodes (7.7%), three infusions were required; for two episodes (3.8%), four infusions were required; and in 1 episode (1.9%), five infusions were required for resolution. All bleeding episodes occurred while subjects were on prophylaxis and the majority were minor bleeding episodes. There were no major bleeding episodes and four moderate bleeding episodes including three moderate episodes of hematuria and one moderate compression fracture with associated bleeding.

There were no surgeries performed during the study in subjects <12 years of age. Extrapolation was performed from subjects ≥ 12 year of age from study IB1001-01 (NCT00768287) who underwent perioperative management with Ixinity with acceptable efficacy outcomes. This included 19 major surgeries in subjects ≥ 12 years of age, including three adolescent pediatric subjects ages 12, 14, and 16.

Safety Results

The clinical safety was assessed by monitoring AEs, vital signs, laboratory parameters, immunogenicity markers, and thrombogenicity markers. The total safety analyses included all 21 subjects enrolled.

Sixteen (76%) subjects were reported to have at least one treatment-emergent adverse event (TEAE). Two subjects (9.5%) had serious TEAEs including hematuria and spinal compression fracture. Both serious TEAEs were considered unrelated to study drug. One subject (4.8%) had a TEAE (hypersensitivity) that was assessed as possibly related to the study drug; and 2 subjects (9.5%) had TEAEs (hypersensitivity and spinal compression fracture) that led to study termination. All non-serious TEAEs were resolved. There were no deaths in the study. No subject had a dose reduction or temporary discontinuation in study drug due to a TEAE.

Of the 16 subjects who experienced TEAEs, there was 1 severe TEAE, 7 moderate TEAEs in 4 subjects, and 41 mild TEAEs in 11 subjects. Of the 21 subjects in the safety analysis population, 11 (52.4%) experienced mild AEs, 4 (19%) experienced moderate AEs, and 1 (4.8%) experienced severe AEs (hematuria and spinal compression fracture).

The most common TEAEs were infections (57.1%), including nasopharyngitis, bronchitis, influenza, viral respiratory tract infection, respiratory tract infection, and tonsillitis; and respiratory, thoracic, and mediastinal disorders (23.8%), including oropharyngeal pain and rhinorrhea.

FIX inhibitor formation was not observed. Non-inhibitory FIX antibodies were seen in three subjects and anti-CHOPP antibodies were seen in three subjects. For the subjects with non-inhibitory FIX antibodies, one subject tested positive at screening and throughout the study. The other two subjects' responses were sporadic and transient. All the subjects with anti-CHOPP antibodies had sporadic and transient responses. There was no correlation between the subjects with non-inhibitory FIX antibodies and anti-CHOPP antibodies. These subjects did not have efficacy or safety concerns identified during the study.

One subject experienced a non-serious hypersensitivity reaction assessed as possibly related to Ixinity, which led to study termination. The subject did not test positive for either non-inhibitory FIX antibodies or anti-CHOPP antibodies at all visits. There were no reports of anaphylaxis or other serious allergic-type reactions.

In the pivotal adult trial, a higher-than-expected number of subjects had anti-CHOPP antibodies. Subjects with high titers stopped treatment and the study was placed on clinical hold in the United States at that time. Due to these findings, an additional manufacturing step in the production of Ixinity was implemented, removing immunogenic host cell proteins to reduce the potential for anti-CHOPP antibodies. Subsequent subjects enrolled in trials received this modified product. A risk analysis assessment addressing potential safety concerns was performed during the pivotal study. The risk assessment analysis of non-inhibitory FIX antibodies and anti-CHOPP antibodies in the pivotal trial showed no associated clinical findings

including no AEs, lack of therapeutic effect, or alterations in PK in study subjects that developed these antibodies.

Reviewer Comment: The benefit-to-risk profile for Ixinity in children remains favorable despite indeterminate-titer non-inhibitory binding antibodies to FIX and CHOPP as there was no observed clinical significance.

The PK analyses included 20 subjects and showed a 20% lower recovery and a 33% higher clearance (CL) than in subjects ≥ 12 years of age treated with Ixinity. The half-life was 15.9 hours in subjects < 6 years of age and 16.8 hours in subjects 6 to < 12 years of age compared with 24 hours in subjects ≥ 12 years of age. The starting dose of 35 to 75 IU/kg was based on the recovery during the PK phase recommended for children < 12 years of age. Dose adjustment of Ixinity based on clinical response is recommended in subjects < 12 years of age due to lower recovery, shorter half-life, and higher CL in this study.

Conclusion

Ixinity is effective in preventing bleeding in pediatric subjects with hemophilia B on a twice-weekly prophylaxis dose. It is also effective in the treatment of bleeding episodes and perioperative management. The Applicant has provided substantial evidence of effectiveness and safety based on a single adequate and well-controlled clinical investigation providing compelling evidence of clinical benefit supported by the initial clinical investigation and preclinical studies. The overall benefit-risk assessment is favorable, and the clinical review team recommends regular approval for the use of Ixinity for on-demand treatment and control of bleeding episodes, perioperative management, and routine prophylaxis to reduce the frequency of bleeding episodes in children < 12 years of age with hemophilia B.

Recommendation

An approval is recommended.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

APVO101-903 provides the basis of approval of Ixinity for on-demand treatment and control of bleeding episodes, perioperative management, and routine prophylaxis to reduce the frequency of bleeding episodes in children < 12 years of age with hemophilia B. The age at screening in the full analysis set ($n = 21$) and the safety set ($n = 21$) ranged from 1 to 10 years of age with a mean age of 6.2 years. Ten subjects were < 6 years of age and 11 subjects were 6 to < 12 years of age. The population was 100% male, 85.7% White, 14.3 % Black, and 9.5% Hispanic.

1.2 Subject Experience Data

Subject rating of treatment with Ixinity at the bleeding episode level was a secondary efficacy endpoint. For each bleeding episode, subjects or their caretaker were asked to rate the efficacy of Ixinity on a four-point scale of “excellent” to “poor,” according to the following definitions:

- Excellent: a dramatic response with abrupt pain relief and clear reduction in joint or hemorrhage site size.
- Good: pain relief or reduction in hemorrhage site size that may have required an additional infusion for resolution.
- Fair: probable, or slight beneficial response usually requiring one or more additional infusions for resolution.
- Poor: no improvement or condition worsens.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

FIX deficiency (hemophilia B, Christmas disease) is the second most common coagulation factor deficiency. Deficiency of the essential blood coagulation FIX results in impaired hemostasis and increased bleeding tendency. The hemophilia B gene is located on the X chromosome with an X-linked recessive inheritance pattern, affecting 1 in 100,000 male births and is rare in females. Hemophilia B is divided into groups based on FIX levels that correlate with the disease pattern. Severe disease is defined as <1% circulating FIX; moderate at 1% to 5%; and mild at >5%. A goal of modern hemophilia management is to prevent spontaneous bleeds by supplying replacement factor prophylactically to maintain higher FIX activity levels.

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

Treatments for hemophilia B require replacement with a form of FIX. FIX therapy includes human plasma products such as fresh-frozen plasma or prothrombin complex concentrates. Monoclonally purified, recombinant FIX preparations are also available and are the mainstay of therapy. Hemgenix (Etranacogene dezaparvovec) is the first and only gene therapy product for hemophilia B, approved in November 2022.

2.3 Safety and Efficacy of Pharmacologically Related Products

FDA-approved recombinant FIX products include Benefix approved in 1997, Rixubis approved in 2013, Alprolix approved in 2014, Ixinity approved in 2015, Idelvion approved in 2016, and Rebinyn approved in 2017. There are two approved plasma-derived FIX products include: Alphanine and Mononine.

The following excerpts are from the package inserts (PIs) of products specifically approved for Von Willebrand disease:

Benefix

- Efficacy: Indicated for hemophilia B in adults and children for on-demand treatment and control of bleeding episodes and perioperative management of bleeding, and in subjects ≥16 years of age for routine prophylaxis to reduce the frequency of bleeding episodes.
- Safety: The most common adverse reactions (incidence >5%) from clinical trials were fever, cough, nausea, injection site reaction, injection site pain, headache, dizziness, and rash.

Rixubis

- Efficacy: Indicated for hemophilia B in adults and children for control and prevention of bleeding episodes, perioperative management, and routine prophylaxis.
- Safety: Common adverse reactions (incidence >1%) in clinical trials were dysgeusia, pain in extremity, and positive test for furin antibody.

Alprolix

- Efficacy: Indicated for hemophilia B in adults and children for on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis to reduce the frequency of bleeding episodes.
- Safety: Common adverse reactions (incidence $\geq 1\%$) in PTPs from clinical trials were headache, oral paresthesia, and obstructive uropathy. Common adverse reactions (incidence $\geq 1\%$) in previously untreated subjects from clinical trials were FIX inhibition, injection site erythema, and hypersensitivity.

Idelvion

- Efficacy: Indicated for hemophilia B in adults and children for on-demand treatment and control of bleeding episodes, perioperative management of bleeding, routine prophylaxis to reduce the frequency of bleeding episodes.
- Safety: The most common adverse reactions (incidence $\geq 1\%$) in clinical trials were headache, dizziness, hypersensitivity, and rash.

Rebinyn

- Efficacy: Indicated for hemophilia B in adults and children for on-demand treatment and control of bleeding episodes and perioperative management of bleeding.
- Safety: The most frequently reported adverse reactions (incidence $\geq 1\%$) were itching and injection site reactions. Animals administered repeat doses of Rebinyn showed accumulation of polyethylene glycol in the choroid plexus. The potential clinical implications of these animal findings are unknown. It is not indicated for routine prophylaxis in the treatment of subjects with hemophilia B due to this unknown.

Alphanine

- Efficacy: Indicated for hemophilia B in adults and children for prevention and control of bleeding.
- Safety: No adverse reactions in the trial. Adverse reactions to plasma-derived products can include allergic reactions, mild chills, nausea, or stinging at the infusion site.

Mononine

- Efficacy: Indicated for hemophilia B in adults for prevention and control of bleeding.
- Safety: Five subjects experienced alanine transaminase elevations. Adverse reactions to plasma-derived products can include allergic reactions, headache, fever, chills, flushing, nausea, vomiting, tingling, lethargy, hives, and stinging or burning at the infusion site.

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

Ixinity was approved in April 2015 for the control and prevention of bleeding episodes and perioperative management in subjects ≥ 12 years of age with hemophilia B in the United States. The initial Biologics License Application (BLA) was approved based on studies IB1001-01, IB1001-01 (using modified-Ixinity), and IB1001-02.

In September 2020, an additional indication for routine prophylaxis to reduce the frequency of bleeding episodes in adults and adolescents ≥ 12 years of age with hemophilia B was approved in the United States.

Ixinity has been extensively studied and used for treatment of hemophilia B in the United States, Europe, South America, Canada, Israel, and Africa.

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

The evidence for safety and efficacy for this product was collected under IND 13551, BLA 125426/0, BLA 125426/177, and sBLA 12426/223.

- The Initial BLA submission was April 6, 2012. Complete response letters were issued on February 1, 2013, and July 29, 2014, due to chemistry, manufacturing, and controls (CMC; manufacturing and inspectional) issues. Clinical trials were put on clinical hold in July 2012 because of immunogenicity (anti-CHOPP antibodies) concerns. Clinical hold was removed on July 26, 2013, and subsequent subjects received modified product.
- On April 29, 2015, Ixinity was approved for the control and prevention of bleeding episodes and perioperative management in subjects ≥ 12 years of age with hemophilia B in the United States. Prophylaxis was not approved due to exclusivity restrictions as Rixubis for prophylaxis was granted orphan exclusivity on June 26, 2013.
- On September 25, 2020, an additional indication for routine prophylaxis to reduce the frequency of bleeding episodes in adults and adolescents ≥ 12 years of age with hemophilia B was approved in the United States. The prior block due to Rixubis having orphan exclusivity for prophylaxis expired June 26, 2020, for subjects ≥ 12 year of age.
- On February 17, 2021, this approval for prophylaxis to reduce the frequency of bleeding episodes was rescinded for adolescents 12 to 17 years of age due to Rixubis having orphan drug exclusivity for this age group through September 12, 2021. This indication was then reinstated November 7, 2022, after the Rixubis orphan exclusivity expired.

Pediatric Regulatory History

- In the approval letter for Ixinity issued April 29, 2015, the Applicant was instructed to reopen pediatric trial IB1001-02 to fulfill the requirements in the pediatric study proposals. The agency requested that the Applicant submit PK, safety, and efficacy data on 20 pediatric PTPs < 12 years of age with 50 EDs as a post-marketing requirement (PMR).
- The Applicant requested a change to Pediatric Research Equity Act (PREA) PMR due to revision of the pediatric study protocol, which was granted on January 20, 2016, with a revised study completion date of June 2018. The Applicant then requested that the agency consider the PMR fulfilled based on data from 12 pediatric subjects that were initially treated under the original BLA. The review team did not agree with the Applicant's plan. The Applicant's request was presented to Pediatric Review Committee (PeRC) on August 8, 2018, and found to be unacceptable.
- In October 2018, a deferral extension was granted by the Agency in concurrence with PeRC. The revised milestones included pediatric study completion date by June 29, 2018, with final clinical study report due December 14, 2018. A second deferral extension was then granted with study completion date by June 29, 2021, and final clinical study report due December 14, 2021. A third deferral extension was then granted with final clinical study report due January 30, 2023. Finally, a final deferral was granted with the final study report due June 30, 2023, which was fulfilled and is the trigger for the current review by PeRC.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

Submission quality and completeness were acceptable from the clinical perspective.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The Applicant noted that the study complied with good clinical practices. There were no clinical study conduct or data integrity issues that impacted the clinical review of this submission.

3.3 Financial Disclosures

The original Applicant/Sponsor was Aptevo BioTherapeutics LLC. On February 28, 2020, Medexus Pharmaceutical, Inc. acquired Aptevo BioTherapeutics and obtained all rights to APVO101 (trade name Ixinity), including the APVO101-903 clinical trial and applications.

Covered clinical study (name and/or number):
Was a list of clinical investigators provided? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request list from applicant)
Total number of investigators identified: <u>12</u>
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>None</u>
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>None</u>
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)): Not applicable Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____ Is an attachment provided with details of the disclosable financial interests/arrangements? <input type="checkbox"/> Yes <input type="checkbox"/> No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? <input type="checkbox"/> Yes <input type="checkbox"/> No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): Not applicable Is an attachment provided with the reason? <input type="checkbox"/> Yes <input type="checkbox"/> No (Request explanation from applicant)

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

4.1 Chemistry, Manufacturing, and Controls

There were no significant CMC issues for this supplement. Please see CMC review memo for further details.

4.2 Assay Validation

There was no issue related to assay validation for this supplement.

4.3 Nonclinical Pharmacology/Toxicology

There were no significant nonclinical pharmacology/toxicology issues for this supplement.

4.4 Clinical Pharmacology

The clinical pharmacology section of this efficacy supplement included APVO101-903, a single phase 3/4 prospective, single-arm, open-label, uncontrolled, multicenter study evaluating the safety, efficacy, and PK of Ixinity prophylaxis in PTPs <12 years of age with severe or moderately severe hemophilia. Administration of Ixinity led to immediate correction of FIX deficiency. The observed half-lives in APVO101-903 pediatric subjects (<12 years of age) were shorter than those observed previously with Ixinity in a population including older subjects (≥12 years of age) at 15.9 (1.4) hours for subjects <6 years of age and 16.8 (2.8) hours for subjects 6 to <12 years of age versus 24 (7) hours in subjects ≥12 years of age. Also shown was a 20% lower recovery and a 33% higher CL than in subjects ≥12 years of age treated with Ixinity. The starting dose of 35 to 75 IU/kg was based on the recovery during the PK phase recommended for children <12 years of age. Dose adjustment of Ixinity based on clinical response is recommended in subjects <12 years of age due to lower recovery, shorter half-life, and higher CL in this study. From a clinical pharmacology standpoint, the efficacy supplement is acceptable to support approval. Please refer to the clinical pharmacology review memo for further details.

4.4.1 Mechanism of Action

FIX is a normal constituent of human plasma. FIX is key for normal hemostasis and plays a significant role within the coagulation cascade. It is located within the blood plasma in its inactivated state. FIX is dependent on the presence of Vitamin K and is activated by the function of Coagulation Factor XIa. After being activated, FIX forms a complex with Factor VIII to activate Coagulation Factor X. The activation of Factor X is an integral step in the blood coagulation cascade and normal blood clotting.

4.4.2 Human Pharmacodynamics (PD)

Please see above 4.4 Clinical Pharmacology.

4.4.3 Human Pharmacokinetics (PK)

Please see above 4.4 Clinical Pharmacology.

4.5 Statistical

The statistical reviewer verified that the primary study endpoint analyses cited by the Applicant were supported. Please see the Statistical Review for further details.

4.6 Pharmacovigilance

Please refer to the Office of Biostatistics and Pharmacovigilance Review Memo for further details.

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

5.1 Review Strategy

The draft PI was reviewed first. This was followed by review of the final study report and datasets for APVO101-903, final study reports submitted to the original BLA and corresponding clinical review memos, responses to clinical information requests seeking clarification of information in the submission, and financial disclosure forms.

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

Documents for this review were included under IND 13551, BLA 125426/0, BLA 125426/177, and sBLA 12426/223. This includes the Ixinity draft PI annotated changes, clinical study reports and protocols for APVO101-903 and IB1001-01, prior approval and deferral letters/memos for Ixinity, and clinical information request responses from the Applicant. The clinical memos and PIs were also reviewed for Benefix, Rixubis, Alprolix, Idelvion, Rebinyn, Alphanine, and Mononine.

5.3 Table of Studies/Clinical Trials

Data from APVO101-903 study is used as the basis of approval for this efficacy supplement. There were 10 study sites in Brazil, Georgia, Moldova, South Africa, Turkey, and Ukraine. Data from IB1001-01 was also reviewed to support efficacy. The study sites were in Israel, Italy, UK, USA, France, India, Poland.

Table 1. Table of Studies and Clinical Trials

Study No.	Population	Design	Treatment	Primary Objective
APVO101-903 (PK Phase)	20 subjects <12 years of age with severe to moderately severe hemophilia B previously treated with FIX replacement therapy	Single phase 3/4 prospective, single-arm, open-label, uncontrolled, multicenter study assessing PK, safety, and efficacy	PK phase Initial PK evaluation – single dose of Ixinity PK phase dose A single infusion of 75 ± 5 IU/kg	PK endpoints: Incremental recovery, IVR, AUC _{0-∞} , AUC _{0-t} , MRT, λZ, t _{1/2} , CL, and Vd _{ss} .
APVO101-903 (Treatment Phase)	21 subjects <12 years of age with severe to moderately severe hemophilia B previously treated with FIX replacement therapy	Single phase 3/4 prospective, single-arm, open-label, uncontrolled, multicenter study assessing PK, safety, and efficacy	Treatment phase Ixinity prophylaxis treatment for 50 EDs Treatment phase dose: Ixinity twice weekly or at a frequency determined appropriate by the investigator for prophylaxis. The starting prophylaxis dose was based on recovery and is ideally within the recommended dose range of 35-75 IU/kg Dose range for treatment of bleeding episodes: Minor or moderate bleeds: 40-60 IU/kg Major or life-threatening bleeds: 60-100 IU/kg	Safety endpoints: Adverse events, inhibitory FIX antibodies, non-inhibitory FIX antibodies, anti-CHOPP antibodies, thrombogenic markers. Efficacy endpoint: ABR.
APVO101-903 (Continuation Phase)	19 subjects <12 years of age with severe to moderately severe hemophilia B previously treated with FIX replacement therapy	Single phase 3/4 prospective, single-arm, open-label, uncontrolled, multicenter study assessing PK, safety, and efficacy	Continuation phase: Ixinity prophylaxis treatment for additional ≥50 ED Continuation phase dose for prophylaxis and bleeding episodes: Same as treatment phase above	Safety endpoints: Adverse events, inhibitory FIX antibodies, non-inhibitory FIX antibodies, anti-CHOPP antibodies, thrombogenic markers. Efficacy endpoint: ABR.

Study No.	Population	Design	Treatment	Primary Objective
APVO101-903 (Surgery Assessment)	Subjects undergoing surgery during the treatment and continuation phases N = 0 enrolled	Single phase 3/4 prospective, single-arm, open-label, uncontrolled, multicenter study assessing PK, safety, and efficacy	Dose for surgery: • Bolus infusion: Loading dose up to 120 IU/kg, followed by 60 IU/kg at 12 hours and up to 120 IU/kg at 24 hours then every 12 hours for ≥ 3 days for major or ≥ 1 day for minor. • Continuous infusion: target plasma level of FIX 70%-110% for ≥ 3 days for major surgery or > 1 day for minor surgery	Surgery endpoints: Surgeon assessment of estimated blood loss at time of surgery, surgeon assessment of post-surgery blood loss (at 12-hours and 24-hours post-surgery timepoints).
IB1001-01 (PK Phase)	32 subjects ≥ 12 years of age with severe hemophilia B and a history of frequent bleeding episodes previously treated with FIX replacement therapy for ≥ 150 ED	Randomized, double-blind, crossover multicenter study using Benefix as comparator assessing PK	PK phase dose: a single infusion of 75 ± 5 IU/kg	PK Endpoints: Non-inferiority to Benefix as assessed by C_{max} , AUC to 72 hours and total CL, rate of elimination for terminal phase, terminal half-life, IVR, incremental recovery, MRT, V_{dss} .
IB1001-01 (Treatment Phase)	68 subjects ≥ 12 years of age with severe hemophilia B previously treated with FIX replacement therapy for ≥ 150 ED	Open-label, uncontrolled trial of safety and efficacy Treatment ≥ 50 ED	Treatment phase: Ixinity prophylaxis treatment for ≥ 50 ED Treatment phase dose: Ixinity with initial dose of 50-75 IU/kg twice weekly. May be adjusted at discretion of investigator. Subjects could also switch between OD and prophylaxis at investigator discretion Dose range for treatment of bleeding episodes: 50-100 IU/kg with repeat doses administered as needed to achieve hemostasis	Safety endpoints: Acute effects associated with infusions inhibitor development, adverse events within 72 hours of study products. Efficacy endpoints: Breakthrough bleeding during prophylaxis, control of bleeding while on prophylaxis and on-demand

Study No.	Population	Design	Treatment	Primary Objective
IB1001-01 (Continuation Phase)	45 subjects ≥ 12 years of age with severe hemophilia B previously treated with FIX replacement therapy for ≥ 150 ED	Open-label, uncontrolled trial of long-term safety and efficacy	Continuation phase: Ixinity prophylaxis treatment for up to 100 ED Continuation phase dose: Same as treatment phase above	Endpoints: Long-term safety and efficacy
IB1001-01 (Surgery sub-study)	17 subjects ≥ 12 years of age with severe hemophilia B previously treated with FIX replacement requiring major surgery	Open-label, uncontrolled trial	Dose for surgery • Bolus infusion: loading dose up to 120 IU/kg within 1 hour prior to surgery, followed by bolus dosing cumulatively totaling 60 IU/kg at 12 hours and up to 120 IU/kg at 24 hours after the first infusion. Continue every 12 hours for a minimum of 3 days • Continuous infusion: target plasma level of FIX between 70% and 110% for a minimum of 3 days post-procedure	Efficacy endpoints: Estimated blood loss during surgery, post-surgery blood loss

Source: CSRs for APVO101-903 and IB1001-01.

Abbreviations: ABR, annualized bleeding rate; Anti-CHOPP, anti-Chinese hamster ovary cell proteins; AUC_{0-t}, area under the plasma concentration curve from time 0 to time; AUC_{0-∞}, area under the plasma concentration curve from time 0 to infinity; CL, clearance; C_{max}, maximum post-infusion plasma concentration; ED, exposure day; FIX, Factor X; IVR, in vivo recovery; MRT, mean residence time; PK, pharmacokinetics; T_{1/2}, terminal half-life; V_{d_{ss}}, volume of distribution at steady-state, λ_Z, elimination rate constant.

5.4 Consultations

PeRC

In the approval letter for Ixinity issued April 29, 2015, the Applicant was instructed to reopen pediatric trial IB1001-02 (now APVO101-903) to fulfill the requirements in the pediatric study proposals. The agency requested that the Applicant submit PK, safety, and efficacy data on 20 pediatric PTPs <12 years of age with 50 EDs as a PMR.

The Applicant requested a change to PREA PMR, due to revision of the pediatric study protocol, which was granted on January 20, 2016, with a revised study completion date of June 2018. The Applicant then requested that the agency consider the PMR to be fulfilled based on the data from 12 pediatric subjects that were initially treated under the original BLA. The review team did not agree with the Applicant's plan. The Applicant's request was presented to PeRC on August 8, 2018, and found to be unacceptable.

In October 2018, a deferral extension was granted by the Agency in concurrence with PeRC. This was the first of 4 deferrals.

Original Milestones

- Final protocol submission: June 17, 2014
- Study completion date: September 30, 2017
- Final report submission: December 31, 2017

First Deferral (January 20, 2016)

- Final protocol submission: Nov 6, 2015
- Clinical Study IB1001-02B completion date: June 29, 2018
- Final clinical study report: December 14, 2018

Second Deferral (October 17, 2018)

- Pediatric study completion date: June 29, 2021
- Pediatric final clinical study report due: December 14, 2021

Third Deferral (July 26, 2022)

- Pediatric study completion date: June 29, 2021
- Pediatric final clinical study report due: January 30, 2023

Fourth and final Deferral (March 23, 2023)

- Pediatric study completion date: June 29, 2021
- Pediatric final clinical study report due: June 30, 2023 (fulfilled)

The final clinical study report was submitted by due date June 30, 2023, fulfilling PREA PMR and was the trigger for the current review by PeRC. This was presented and reviewed at PeRC on January 23, 2024. Both the Division of Clinical Hematology Evaluation and PeRC agreed that the current study report and clinical review fulfills the PREA PMR deferred from 2015.

5.5 Literature Reviewed (if applicable)

European Medicines Agency, 2018, Clinical investigation of recombinant and human plasma-derived factor IX products - Scientific guideline, accessed February 26, 2024, <https://www.ema.europa.eu/en/clinical-investigation-recombinant-human-plasma-derived-factor-ix-products-scientific-guideline>.

Montgomery, RR, JC Gill, and JP Scott, 2014, Hemophilia and von Willebrand's Disease, Nathan and Oski's Hematology of Infancy and Childhood, Nathan, D. G., S. H. Orkin, D. Ginsberg and A. T. Look, 6th edition, Philadelphia: WB Saunders.

World Federation of Hemophilia, 2020, Guidelines for the Management of Hemophilia, accessed February 26, 2024, 2024, <https://guidelines.wfh.org/>.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

APVO101-903: Single phase 3/4 prospective, single-arm, open-label, uncontrolled, multicenter study evaluating the safety, efficacy, and PK of APVO101 prophylaxis in subjects in PTPs <12 years old with severe or moderately severe hemophilia.

6.1.1 Objectives

Primary Objectives

- Evaluate the safety of Ixinity in pediatric subjects <12 years of age with hemophilia B for at least 50 ED.
- Assess the efficacy of Ixinity prophylaxis with respect to prevention of breakthrough bleeding and with respect to control of hemorrhage.
- Evaluate the PK of Ixinity.
- Evaluate Ixinity immunogenicity response.

Secondary Objectives

- Evaluate the efficacy of the treatment of breakthrough bleeds from subjects and investigators.

Exploratory Objectives

- Evaluate markers of thrombogenicity.
- Evaluate efficacy for perioperative management.

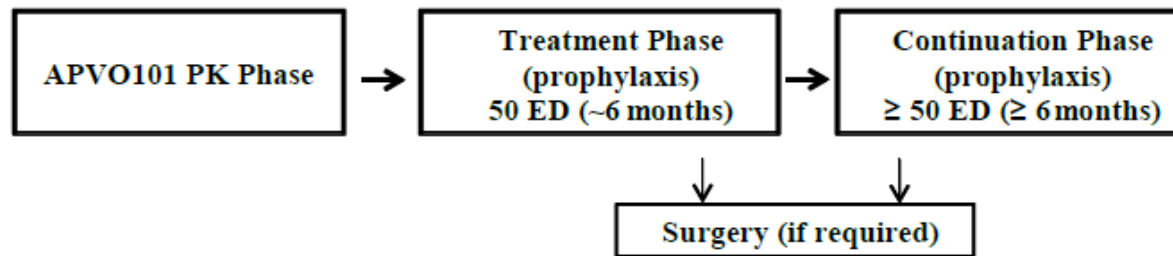
6.1.2 Design Overview

APVO101-903 is a prospective, non-controlled, international, multi-center phase 3/4 study investigating the PK, efficacy, and safety of Ixinity in PTPs <12 years of age with severe to moderately severe hemophilia B for at least 50 EDs. Planned enrollment was up to 22 subjects to have 15 to 20 evaluable subjects complete a minimum of 50 EDs. Duration of the study was to be at least 12 months.

It consisted of 3 distinct phases:

- PK phase: All subjects were to undergo PK assessments up to 50 hours during the PK phase of the study.
- Treatment phase: After completion of the PK phase, subjects were to start prophylaxis. Prophylaxis dose based on recovery and ideally within recommended dose range 35 to 75 IU/kg twice weekly. The planned treatment duration during the treatment phase per subject was 50 EDs.
- Continuation phase: After completion of the treatment phase, subjects were to continue prophylaxis for an additional ≥50 EDs.

Figure 1. APVO101 Study Design



Source: APVO101-903 protocol page 29.
Abbreviations: ED, exposure day; PK, pharmacokinetic.

6.1.3 Population

Inclusion Criteria

1. Age: <11.5 years of age at the time of the first dose and <12 years of age throughout the treatment phase of the study (for at least 50 EDs).
2. Informed consent: subject's parent or legal guardian written Institutional Review Board /Ethics Committee-approved informed consent. An assent form (Institutional Review Board /Ethics Committee-approved) will be obtained, when required by local regulations/guidelines.
3. Willingness and ability to make the required study visits and follow instructions while enrolled in the study (for at least 50 EDs; approximately 6 months).
4. Documented severe or moderately severe hemophilia B diagnosis (FIX activity ≤ 2 IU/dL); in addition, severity may be indicated by the occurrence of one or more joint bleeding episode(s) at any point in the child's medical history requiring infusion(s) to replace FIX.
5. Subjects must be on prophylaxis or switch to a prophylaxis regimen for the duration of the study.
6. PTPs with a minimum of 50 EDs (as documented and determined by the investigator) to a preparation/blood components containing FIX.
7. Willingness to adhere to the four-day washout period of any FIX replacement therapy prior to PK evaluation. In case of previous exposure to a FIX product with a prolonged half-life, a washout period of three half-lives is required to achieve steady state FIX level prior to exposure to Ixinity.
8. Immunocompetent (CD4 count $>400/\text{mm}^3$) and not receiving immune modulating or chemotherapeutic agents.
9. Platelet count at least $150,000/\text{mm}^3$.
10. Liver function: alanine transaminase and aspartate transaminase ≤ 2 times the upper limit of the normal range.
11. Total bilirubin ≤ 1.5 times the upper limit of the normal range.
12. Renal function: serum creatinine ≤ 1.25 times the upper limit of the normal range.
13. Hemoglobin ≥ 7 g/dL.

Exclusion Criteria

1. History of FIX inhibitor ≥ 0.6 Bethesda Units.
2. Existence of another coagulation disorder.
3. Evidence of thrombotic disease, fibrinolysis, or disseminated intravascular coagulation.
4. Use of an investigational drug within 30 days prior to study entry.

5. Previous use of Ixinity.
6. Use of medications that could impact hemostasis, such as aspirin.
7. Known hypersensitivity to the active substance or to any of the excipients in the investigational products.
8. Known allergic reaction to hamster proteins.
9. History of poor compliance, geographic isolation, unreliable transportation, a serious medical or social condition, or any other circumstance that, in the opinion of the investigator, would interfere with participation or compliance with the study protocol.
10. History of adverse reaction to either plasma-derived FIX or recombinant FIX that interfered with the subject's ability to treat bleeding episodes with a FIX product.
11. History of any medical condition that would impact the efficacy evaluation and/or safety evaluation of the study product.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The FIX concentrate Ixinity, produced in a CHOPP line, was presented as a powder and solvent for intravenous injection in single-use vials containing nominally 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU, and 3000 IU per vial.

Ixinity dosage for baseline PK assessment in pediatric subjects <12 years of age: Single dose of 75 ± 5 IU/kg body weight.

Ixinity dosage for prophylactic treatment in subjects <12 years of age: The starting prophylaxis dose was to be determined based on Ixinity recovery, ideally within the recommended dose range of 35 to 75 IU/kg twice weekly for 50 EDs (approximately 6 months) in the treatment phase and an additional ≥ 50 EDs in the continuation phase. Prophylaxis was to start after completion of the PK phase.

Ixinity dosage for the treatment of breakthrough bleeding episodes in treatment and continuation phases was determined based on severity of the bleeding episode.

Minor bleeding episodes defined as: uncomplicated hemarthroses and superficial muscle (except iliopsoas) with no neurovascular compromise, and other soft tissue. Treatment dose 40 to 60 IU/kg.

Moderate bleeding episodes defined as: hemarthrosis of longer duration, recurrent hemarthrosis, mucous membranes, deep lacerations, and hematuria. Treatment dose 40 to 60 IU/kg.

Major or life-threatening bleeding episodes defined as: iliopsoas, deep muscle with neurovascular injury, substantial blood loss, central nervous system, pharyngeal, retropharyngeal, and retroperitoneal. Treatment dose 60 to 100 IU/kg.

Dose modifications were determined by the investigator based on:

- Pre- and/or post-dose FIX activity
- Type and severity of the bleeding episode
- Occurrence of an injury
- Timing of the infusion relative to the onset of bleeding
- Degree of pain, swelling, and disability at the site
- Dosage of and clinical response to the first infusion
- Follow-up infusion(s) given and timing of the follow-up infusion(s)
- Re-injury, or injury at a previous site of bleeding such as a target joint

Pre- and post-Ixinity infusion FIX activity was recommended to determine dose modifications. The reason for dose modifications was to be recorded in the case report form.

For surgical prophylaxis, bolus and continuous infusions were allowed and determined by the investigator and surgeon. Recommended is listed dosing below.

Bolus Infusions

- Initial dose: up to 120 IU/kg within 1 hour prior to surgery.
- Subsequent dosing: 60 IU/kg 12 hours after the first infusion up to 120 IU/kg 24 hours after the first infusion depending on the subject’s post-infusion FIX activity.
- Bolus infusions will continue every 12 hours as long as the investigator and surgeon deem necessary, but for a minimum of ≥3 days post-procedure for major surgery or a ≥1-day post-procedure for minor surgery.

Continuous Infusions

- Infusion rate, dose, and timing of subsequent infusions and adjustments in dosing guided by FIX assay results with the doses of Ixinity administered appropriately to ensure that the plasma FIX level does not drop below 60% and is within range of 70% and 110%.
- Length of treatment determined by investigator and surgeon but for a minimum ≥3 days post-procedure for major surgery or a ≥1 day post-procedure for minor surgery.

Table 2. Study Intervention Administered

Phase and Regimen	Strength
PK phase Following 4-day washout from previous FIX replacement or 3 half-lives of previous FIX products with prolonged half-life	Single IV 75 (±5) IU/kg dose of Ixinity
Treatment phase Prophylaxis	Single IV 35-75 IU/kg dose of Ixinity twice weekly or at a frequency determined as appropriate by the Investigator
Minor/moderate bleeding episodes	Ixinity IV 40-60 IU/kg (single dose)
Major/life-threatening bleeding episodes	Ixinity IV 60-100 IU/kg (single dose)
Continuation phase Prophylaxis	Single IV 35-75 IU/kg dose of Ixinity twice weekly or at a frequency determined as appropriate by the Investigator
Minor/moderate bleeding episodes	Ixinity IV 40-60 IU/kg (single dose)
Major/life-threatening bleeding episodes	Ixinity IV 60-100 IU/kg (single dose)

Phase and Regimen	Strength
Surgery Bolus	Up to IV 120 IU/kg dose of Ixinity 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 every 12 hours 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: APVO101-903 Clinical Study Report page 30
 Abbreviations: FIX, factor IX; IV, intravenous; PK, pharmacokinetic.

6.1.5 Directions for Use

See above 6.1.4 Study Treatments or Agents Mandated by the Protocol

6.1.6 Sites and Centers

The study was conducted at 10 sites in 6 countries: Brazil, Georgia, Moldova, South Africa, Turkey, and Ukraine. Enrolling sites include:

1. Universidade Estadual de Campinas - Centro de Hematologia e Hemoterapia – HEMOCENTRO de Campinas. Campinas, Sao Paulo, Brazil.
2. Centro Estadual de Hemoterapia e Hematologia do Espírito Santo (HEMOES). Vitoria, Espírito Santo, Brazil.
3. Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo. Ribeirão Preto, Sao Paulo, Brazil.
4. JSC K. Eristavi National Center for Experimental and Clinical Surgery. Tbilisi, Georgia.
5. PMSI Institute of Mother and Child. Chisinau, Republic of Moldova.
6. Haemophilia Comprehensive Care Centre. Johannesburg, Gauteng, South Africa.
7. Worthwhile Clinical Trials, Lakeview Hospital. Benoni, Gauteng, South Africa.
8. Ege University School of Medicine University Cd. Izmir, Bornova, Turkey.
9. Cukurova University School of Medicine. Adana, Balcali, 01130, Turkey.
10. National Specialized Children’s Hospital. Kyiv, Ukraine.

6.1.7 Surveillance/Monitoring

The safety of this study was reviewed by an independent data and safety monitoring board. The Safety Monitoring Committee (SMC) was composed of a PSI Medical Monitor/Chairperson, Principal Investigator, and a Medexus Pharma Surveillance Officer. Other members that were invited to the safety review meetings but were not part of the decision making included a PSI Clinical Project Manager and Medexus Pharma Clinical Trial Manager. The SMC met via teleconference at least once on an annual basis during the trial and on an ad-hoc basis to review safety information at the request of any of the SMC members based on the review of the safety information provided by the PSI Data Manager. Screening assessments were provided in Table 3 and Table 4 of the protocol document (see below).

Table 3. Schedule of Events for APVO101-903

Evaluation	Screening	Pre-infusion^a	Post-infusion^a	5 ED (±1 ED)^b	12 ED (±1 ED)^b	25 ED (±1 ED)^b	50 ED (±1 ED)^b	75 ED (±5 ED)^c	100 ED (±5 ED)^c	Every 3 Months (~25 ED ±5 ED)^c	End of Study or Early Termination
Informed consent and/or assent	X										
Eligibility Criteria review	X										
Medical and hemophilia-related history	X	X									
Demographics (age, sex)	X										
FIX mutation	X										
Concomitant medications	X	X		X	X	X	X	X	X	X	X
Physical exam, body weight and height	X	X				X	X	X	X	X	X
Vital signs	X	X	X			X	X	X	X	X	X
Thrombogenic markers		X	X								
CBC with differential	X					X	X	X	X	X	X
CD4 count	X										
Serum chemistry	X					X	X	X	X	X	X
Inhibitor titer and non-inhibitory FIX binding antibodies	X	X		X	X	X	X	X	X	X	X
Anti-CHOPP antibodies	X	X		X	X	X	X	X	X	X	X
Assessment of major and/or target joints	X						X		X		X
Urinalysis	X					X	X	X	X	X	X
FIX activity		X	X								
Adverse events	X		X	X	X	X	X	X	X	X	X

Evaluation	Screening	Pre-infusion^a	Post-infusion^a	5 ED (±1 ED)^b	12 ED (±1 ED)^b	25 ED (±1 ED)^b	50 ED (±1 ED)^b	75 ED (±5 ED)^c	100 ED (±5 ED)^c	Every 3 Months (~25 ED ±5 ED)^c	End of Study or Early Termination
Efficacy/research participant diary	X			X	X	X	X	X	X	X	X
Training on research participant diary and Ixinity reconstitution and administration	X										

Source: APVOIOI-903 Protocol Pages 14-16

a. PK phase

b. Treatment phase

c. Continuation phase

Abbreviations: Anti-CHOPP, anti-Chinese hamster ovary cell proteins; CBC, complete blood count; ED, exposure day; FIX, Factor IX.

Table 4. Schedule of Events for a Surgical Procedure (if Required During Treatment Phase and/or Continuation Phase) in APVO101-903

Evaluation	Prior to surgery: Pre-infusion	Prior to surgery: Post-infusion^a	During Surgery	End of Surgery	12 Hours Post-surgery: Pre-infusion	12 Hours Post-surgery: Post-infusion^a	24 Hours Post-surgery: Pre-infusion	24 Hours Post-surgery: Post-infusion^a	28 Days (±7 Days) Post-FIX Replacement Therapy for Surgery
FIX activity	X	X	X		X	X	X	X	
Inhibitor titer	X								X
Non-inhibitory FIX binding antibodies	X								X
Anti-CHOPP antibodies	X								X
Vital signs	X				X		X		
Adverse events		X	X	X		X		X	
Use of blood products			X	X	X		X		X
Surgeon's assessment of expected/estimated blood loss	X			X	X		X		

Source: APVO101-903 Protocol Pages 14-16

a. 5-30 minutes

Abbreviations: Anti-CHOPP, anti-Chinese hamster ovary cell proteins; FIX, factor IX.

6.1.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint was ABR. ABR was defined as the number of bleeding episodes per year. ABR was calculated for the treatment phase, continuation phase, and then overall for all subjects. The ABR was also compared with the 6 months prior to screening.

The primary safety endpoint was AEs.

The PK endpoints included C_{max} , incremental recovery, in vivo recovery, $AUC_{0-\infty}$, AUC_{0-t} , mean residence time, elimination rate constant, terminal half-life, CL, and volume of distribution at steady-state.

The immunogenicity endpoints included inhibitory FIX antibodies, non-inhibitory FIX antibodies, anti-CHOPP antibodies, and thrombogenic markers.

The secondary efficacy endpoints at the bleeding episode level included 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 secondary efficacy endpoints at the subject level included investigator rating of Ixinity prophylaxis efficacy and investigator rating of Ixinity efficacy for control and management of bleeding episodes.

The exploratory safety endpoints were thrombogenicity markers including D-dimer, TAT, and F1+2 during the first 24 hours post-infusion of Ixinity.

The exploratory efficacy endpoints were for perioperative management in pediatric subjects with hemophilia B including surgeon assessment of estimated blood loss at time of surgery and surgeon assessment of post-surgery blood loss (at 12-hour and 24-hour post-surgery timepoints).

6.1.9 Statistical Considerations & Statistical Analysis Plan

There were no formal sample size considerations. All planned analyses were descriptive in nature. Up to 22 subjects were planned to ensure that at least 15 to 20 evaluable subjects complete the study including completion of PK assessments and a minimum of 50 EDs. The target sample size based on European Medicines Agency regulatory guidelines and the Food and Drug Administration PMR for Ixinity. A total of 21 subjects were enrolled and available for the final analysis for efficacy and safety endpoints.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Inclusion Criteria Included

1. Severe or moderately severe hemophilia B (FIX activity ≤ 2 IU/dL)
2. PTPs with a minimum of 50 EDs to a preparation/blood components containing FIX
3. Subject age at time of screening: <11.5 years of age at the time of the first dose and <12 years of age throughout the treatment phase

Exclusion Criteria Included

1. History of FIX inhibitor ≥ 0.6 Bethesda Units
2. Existence of another coagulation disorder
3. Known hypersensitivity to the active substance or to any of the excipients in the investigational products
4. Known allergic reaction to hamster proteins
5. History of adverse reaction to either plasma-derived FIX or recombinant FIX that interfered with the subject's ability to treat bleeding episodes with a FIX product

6.1.10.1.1 Demographics

Twenty-three subjects were screened with two screen failures. One subject voluntarily withdrew by parent or legal guardian and one subject had an AE of COVID-19 during screening.

Overall, 21 male subjects were enrolled and treated at 10 study sites in 6 countries. Ten subjects were <6 years of age and 11 subjects were 6 to <12 years of age. Twenty subjects had PK assessments that were evaluable. Nineteen subjects completed the treatment phase and went on to the continuation phase. Of those 19 subjects, 15 completed the continuation phase of >100 ED's total and 4 completed between 50 to 100 EDs.

Race

Caucasian: 18 (85.7%)

Black or African American: 3 (14.3%)

Ethnicity

Hispanic or Latino: 2 (9.5%)

Non-Hispanic or Latino: 19 (90.5%)

Table 5. Patient Demographics, APVO101-903

Parameter	Age Group <6 Years (n = 10) n (%)	Age Group 6 to <12 Years (n = 11) n (%)	Total (N = 21) n (%)
Age			
n	10	11	21
Mean	3.3	8.7	6.2
Age Categorized			
<2 years	2 (20.0)	NA	2 (9.5)
≥ 2 years	8 (80.0)	11 (100)	19 (90.5)
Race			
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 Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity			
Hispanic or Latino	1 (10.0)	1 (9.1)	2 (9.5)
Not Hispanic or Latino	9 (90.9)	10 (90.9)	19 (90.5)

Parameter	Age Group <6 Years (n = 10) n (%)	Age Group 6 to <12 Years (n = 11) n (%)	Total (N = 21) n (%)
Gender			
Male	10 (100)	11 (100)	21 (100)
Female	0 (0.0)	0 (0.0)	0 (0.0)
Weight (kg)			
n	10	11	21
Height (cm)			
n	10	11	21
BMI (kg/m ²)			
n	10	11	21

Source: APVOIOI-903 Clinical study Report pages 48-50.
 Abbreviations: BMI, body mass index.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

There were 13 subjects with FIX activity <1% (5 subjects <6 years of age and 8 subjects 6 to 12 years of age) and 8 subjects with FIX activity 1% to ≤2% (5 subjects <6 years of age and 3 subjects 6 to 12 years of age).

The mean ABR was 3.5 during the 6 months prior to enrollment for both age groups (3 in subjects <6 years of age and 3.9 in subjects 6 to <12 years of age).

Eight subjects had medical histories reported. In four of these subjects, these conditions were not ongoing at screening and included anemia, cryptorchism, hypersensitivity, inguinal hernia, and circumcision. One subject had a medical condition that was not ongoing at screening (circumcision) and one that was ongoing at screening (renal aplasia). At screening, ongoing medical conditions in three subjects included moderate anemia, moderate renal aplasia, mild amblyopia, and mild autism spectrum disorder.

A medication was considered concomitant if it was administered after the first study drug administration. The most prescribed concomitant medications were analgesics, antibacterials, antihistamines, cough and cold preparations, antihemorrhagics, anti-inflammatories, antivirals, and corticosteroids. The study excluded subjects with significant concurrent illnesses that could affect safety and/or efficacy analyses. They study also excluded subjects receiving drugs that can affect hemostasis.

6.1.10.1.3 Subject Disposition

All 21 enrolled subjects were included in the final safety and efficacy analyses. Twenty subjects had PK assessments that were evaluable. Nineteen subjects completed the treatment phase and went on to the continuation phase. Of those 19 subjects, 15 completed the continuation phase of >100 EDs total and 4 completed between 50 to 100 EDs. No subjects had surgery during the study.

Major Protocol Deviations

- Visit performed by a sub-investigator not trained and delegated by the principal investigator in one subject.
- Incorrect dose for PK dosing in one subject. Subject excluded from PK analyses.
- Incorrect dose of study medication infused on two occasions in one subject.
- Three doses of study medication omitted in error in one subject.
- Four doses of study medication omitted in error in one subject.
- The site did not perform urinalysis at required visits in three subjects.
- The site did not perform assessment of major and target joint(s) at 50 ED, 100 ED, and end of study in 1 subject.
- Withdraw from the study due to self-administration of alternative therapy of Octanine for the treatment of hemophilia in one subject.

6.1.11 Efficacy Analyses

Twenty subjects out of 21 enrolled were included in the PK analysis during the PK phase at a dose of 75 IU/kg.

Subject (b) (6), 8 years of age, received an incorrect dose of Ixinity at 66 IU/kg instead of the 75 (± 5) IU/kg dose required by the study protocol. This subject was excluded from concentrations and PK parameter descriptive statistics.

Subject (b) (6), 7 years of age, had 1 major deviation from the scheduled time that was later identified. The corresponding concentration was excluded from concentrations descriptive statistics.

Subject (b) (6), 5 years of age, had 3 samples that arrived unfrozen to the bioanalytical lab. These samples were excluded from concentrations and PK parameter descriptive statistics.

Please refer to the clinical pharmacology review memo for PK data and assessment. Of note, the PK analyses showed a 20% lower recovery and a 33% higher CL in subjects <12 years of age treated with Ixinity versus those ≥ 12 years of age. The half-life was 15.9 hours in subjects <6 years of age and 16.8 hours in subjects 6 to <12 years of age compared with 24 hours in subjects >12 years of age. The starting dose of 35 to 75 IU/kg was based on the recovery during the PK phase recommended for children <12 years of age.

Table 6. Pharmacokinetic Parameters Following 75 + 5 IU/kg of Ixinity

Parameters	Age Group <6 Years (n = 10 ^a) Mean (\pm SD) Range	Age Group 6 to <12 Years (n = 10 ^b) Mean (\pm SD) Range	All Subjects <12 Years (n = 20 ^c) Mean (\pm SD) Range	Age Group >12 Years (n = 32) Mean (\pm SD) Range
AUC _{0-∞} (IU/dL/hr)	1118 (\pm 307) 853-1528	1232 (81.7 \pm) 1129-1308	1170 (\pm 231) 853-1528	1573 (\pm 451) 862-2643
Incremental recovery (IU/dL per IU/kg)	0.73 (\pm 0.15) 0.44-0.966	0.85 (\pm 0.15) 0.724-1.09	0.79 (\pm 0.16) 0.44-1.09	0.98 (\pm 0.21) 0.67-1.50 0.67-1.50
Terminal half-life (hours)	15.9 (\pm 1.4) 14.0-17.5	16.8 (\pm 2.8) 13.1-21.2	16.3 (\pm 2.2) 13.1-21.2	24 (\pm 7) 13-43
C _{max} (IU/dL)	56.4 (\pm 13.7) 33-84	63.7 (\pm 9.86) 48-81	60.1 (\pm 12.2) 33-84	73 (\pm 17) 51-113

Parameters	Age Group <6 Years (n = 10 ^a) Mean (±SD) Range	Age Group 6 to <12 Years (n = 10 ^b) Mean (±SD) Range	All Subjects <12 Years (n = 20 ^c) Mean (±SD) Range	Age Group >12 Years (n = 32) Mean (±SD) Range
Mean residence time (hours)	19.9 (±2.48) 16.5-22.8	20.0 (±2.87) 16.3-23.8	20.0 (±2.53) 16.3-23.8	32 (±6) 19-47
Vd _{ss} (mL/kg)	144 (±36.7) 88-179	123 (±18.9) 106-147	134 (±30.6) 88-179	175 (±57) 102-314
Clearance	7.3 (±1.9) 4.91-9.03	6.1 (±0.5) 5.66-6.82	6.8 (±1.5) 4.91-9.03	5.1 (±1.3) 2.8-7.7

Source: Ixinity label page 17-19

a. n = 6, for t_{1/2}, AUC_{0-∞}, MRT, CL, and Vd_{ss}

b. n = 6 for t_{1/2} and n = 5 for AUC_{0-∞}, MRT, CL, and Vd_{ss}

c. n = 12 for t_{1/2} and n = 11 for AUC_{0-∞}, MRT, CL, and Vd_{ss}

Abbreviations: AUC_{0-∞}, area under the plasma concentration curve from time 0 to infinity; CL, clearance; C_{max}, maximum post-infusion plasma concentration; MRT, mean residence time; SD, standard deviation; T_{1/2}, terminal half-life; Vd_{ss}, volume of distribution at steady-state.

Reviewer Comment: Dose adjustment of Ixinity based on clinical response is recommended in subjects <12 years of age due to lower recovery, shorter half-life, and higher CL in this study.

6.1.11.1 Analyses of Primary Endpoint(s)

For prophylactic treatment, Ixinity was to be administered twice weekly or at a frequency determined appropriate by the investigator for the study subject. The starting prophylactic dose for each subject was determined by the recovery from PK phase assessments. Only the pre-infusion and 15 to 30 minutes post-infusion samples were used to determine the starting prophylactic dose. The first prophylactic dose was to be administered after completion of the PK phase. The recommended starting prophylactic dose was 35 to 75 IU/kg twice weekly. The mean prophylaxis dose was 54.8 ± 10.6 IU/kg in subjects <12 years of age (58 ± 8.9 IU/kg in subjects <6 years or age and 52 ± 11.6 IU/kg in subjects 6 to <12 years of age) compared with 55 ± 12.8 IU/kg in subjects ≥12 years of age.

Four of the 10 subjects in the <6 years age group were prescribed once weekly by the investigator.

Subject (b) (6), 5 years of age, received once weekly prophylaxis due to difficulty with infusions and no bleeding episodes the 6 months prior to enrollment. The subject's guardian frequently sought out assistance via emergency services when he was unable to establish vascular access.

Subject (b) (6), 3 years of age, received once weekly prophylaxis. This subject had no bleeding episode in the 6 months prior to enrollment.

Subject (b) (6), 2 years of age, received once weekly prophylaxis. This subject had 1 bleeding episode in the 6 months prior to enrollment.

Subject (b) (6), 1 year of age, was initially prescribed twice weekly prophylaxis. Due to difficult venous access resulting in a hematoma, this subject was switched to once weekly prophylaxis after 2 weeks of starting treatment phase.

ABR was the primary efficacy endpoint. The mean ABR of 2.34 (Table 7) overall in the treatment and continuation phases was lower than the mean historical rate of 3.5. This is

compared with 3.55 in subjects ≥ 12 years of age. The mean ABR was lower in the older age cohort (6 to < 12 years) at 1.19 compared with 3.6 in subjects < 6 years of age.

Table 7. Efficacy of Prophylaxis with Ixinity (N = 21) < 12 Years of Age

Parameter	Result
Total ABR	
Mean \pm SD	2.34 \pm 4.2
Median (IQR)	0.86 (0-1.96)
Spontaneous ABR	
Mean \pm SD	0.63 \pm 1.26
Median (IQR)	0.00 (0-0.85)
Subjects with zero bleeding episodes (%) n	33.3% (7)

*Source: Ixinity Package Insert

Abbreviations: ABR, annualized bleeding rate; IQR, interquartile range; SD, standard deviation.

Reviewer Comment: These results are consistent with improvement and reduction in the bleeding frequency with prophylactic treatment. The product is effective in reducing bleeding when administered as routine prophylaxis in pediatric subjects ≤ 12 years of age with hemophilia B.

6.1.11.2 Analyses of Secondary Endpoints

There was a total of 52 bleeding episodes recorded during the study (treatment and continuation phase) in 14 subjects, 28 bleeds in 6 subjects < 6 years of age and 24 bleeds in 5 subjects 6 to ≤ 12 years of age. The remaining 33% of subjects had no bleeding during prophylaxis with Ixinity. Fifty-four percent of bleeding episodes were injury related, 35% were spontaneous, and 11% were unknown. By site and causality for all bleeds, 22% were joint bleeds and 78% were other bleed types including soft tissue, mucosal, muscle, and hematuria. The mean number of infusions required to treat the bleeding episode was 1.3. In 45 of 52 (86.5%) of the episodes, hemostasis was achieved with zero to two infusions. Four bleeding episodes (7.7%) required three infusions, two episodes (3.8%) required four infusions, and one episode (1.9%) required five infusions for resolution. The majority (92%) of bleeding episodes were minor with only 4 of the 52 bleeding episodes being moderate including 3 episodes of hematuria and 1 moderate compression fracture.

One secondary efficacy endpoint was subject rating of treatment with Ixinity at the bleeding episode level. For each bleeding episode, subjects or their caretaker were asked to rate the efficacy of Ixinity on a four-point scale of excellent to poor. An excellent rating was defined as a dramatic response with abrupt pain relief and clear reduction in joint or hemorrhage site size with; good, pain relief or reduction in hemorrhage site size that may have required an additional infusion for resolution; fair, probable, or slight beneficial response usually requiring one or more additional infusions for resolution; or poor, no improvement or condition worsens. Hemostatic efficacy at bleed resolution was rated as excellent or good in 79% of total bleeds. Fifty-four percent of the bleeding episodes were rated as excellent and 25% as good. No infusions were required to treat the bleeding episode in 17% and efficacy rating was missing in 4%. Bleeds requiring infusions had a mean total dose per bleed of 55.4 IU/kg (median: 54.6 IU/kg, range: 28.6-76.9 IU/kg).

Another secondary efficacy endpoint was investigator rating of Ixinity at the subject level for prophylaxis efficacy and treatment of bleeding episodes. Prophylaxis efficacy was evaluated by the investigator at each ED visit. Ixinity was designated as effective for all subjects at 5, 12, 25, 100, 150, 175, 200, and 225 ED visits, and at the end of study. There was a total of 3 partially

effective ratings in the study, which occurred in 3 subjects (1 each at 50, 75, and 125 ED visit). For treatment of bleeding episodes, Ixinity was rated as effective for all subjects at all ED visits.

Table 8. Summary of Bleeding Episode Level Efficacy Endpoints (Overall), Safety Population

Parameter	Age Group <6 Years (n = 10)	Age Group 6 to <12 Years (n = 10)	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 (53.8)
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)	2 (3.8)
Missing	0 (0.0)	2 (8.3)	2 (3.8)
Time from onset of treatment until resolution of the bleeding episode (min)			
n	17	17	34
Mean	172.4	260.6	216.5
Number of infusions required to treat the bleeding episode as continuous variable			
Mean	28	24	52
Number of infusions required to treat the bleeding episode as categorical variable, n (%)			
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: CSR pages 78-80.

Reviewer Comment: The product showed effective treatment of bleeding episodes from both subject/caretaker and investigator ratings. The product was shown to be effective when used for prophylaxis based on investigator rating of preventing bleeding episodes.

6.1.11.4 Dropouts and/or Discontinuations

There were two TEAEs that led to permanent discontinuations from the study.

One subject, (b) (6) [REDACTED], discontinued due to a moderate non-serious TEAE of hypersensitivity that was designated as possibly related to Ixinity by the investigator. This subject received <50 ED and 13 doses of Ixinity ranging from 43.5 to 76.1 IU/kg. This subject

had two bleeding episodes on the study. One required two infusions until resolution, and one required zero infusions.

A second subject, (b) (6), discontinued due to moderate spinal compression fracture that was considered by the Investigator to be unrelated to Ixinity. The subject had received >50 ED. The subject received five infusions for the spinal compression fracture. The subject had two other bleeding episodes, each requiring one infusion for resolution.

There were no dose reductions or temporary discontinuations of Ixinity due to a TEAE.

6.1.11.5 Exploratory and Post Hoc Analyses

The exploratory efficacy objective was to evaluate the efficacy of Ixinity for perioperative management. The perioperative endpoints were the surgeon's assessment of estimated blood loss at time of surgery and the surgeon's assessment of post-surgery blood loss (at 12-hour and 24-hour post-surgery timepoints).

No surgeries were performed during this study in subjects <12 years of age. The efficacy of perioperative management in children with hemophilia B \geq 12 years of age was evaluated during the pivotal study in adults and can be extrapolated to children <12 years of age. Extrapolation was from subjects \geq 12 years of age from study IB1001-01 who underwent perioperative management with Ixinity with acceptable efficacy outcomes. This included 19 major surgeries in subjects \geq 12 years old, including 3 adolescent pediatric subjects 12, 14, and 16 years of age.

IB1001-01 Surgery Sub-study

A total of 16 evaluable subjects (5 planned) were included for analysis, with 19 major surgery cases (10 planned) performed and included. Subjects were between the 12 to 56 years of age, with a mean age of 33 years. A continuous infusion was used in 6 procedures and bolus infusions were used in 13 procedures. Target FIX levels were achieved with both bolus and continuous infusions. In the 13 procedures in 12 subjects that bolus infusions were given, 78 bolus infusions were used with a mean dose of 60 IU/kg (range 24-120 IU/kg). Mean levels were kept at or above 60%. In the 6 procedures in 4 subjects that continuous infusion was used, the mean loading dose was 95.4 IU/kg (median 99 IU/kg; range 67-109 IU/kg) followed by mean maintenance infusion of 7 IU/kg/hr (median 7 IU/kg/hr; range 3-21 IU/kg/hr). Mean levels were kept between 49% and 142%. Effective hemostasis during and after surgery was obtained with both bolus and continuous infusion regimens. Blood loss during surgery was as expected in 68% of subjects or less than expected in 32% of subjects. Hemostasis at 12 hours and 24 hours were rated as superior or adequate at both time points in 37% and 63%, respectively. No instance of poor hemostasis was recorded. No transfusions during surgery were needed.

Reviewer Comment: While there were no surgeries during this study in subjects <12 years of age, we evaluated the surgery data from subjects \geq 12 years of age from study IB1001-01 who underwent perioperative management with Ixinity with acceptable efficacy outcomes. Also, it is recommended that dosing perioperatively be calculated based on FIX activity levels. Therefore, the review team feels that extrapolation from the data in subjects \geq 12 years of age along with the recommendation to calculate perioperative dosing based on FIX activity levels is adequate for approval for perioperative management indication in subjects <12 years of age.

6.1.12 Safety Analyses

The safety endpoints included:

- AEs
- Inhibitory FIX antibodies
- Non-inhibitory FIX antibodies
- Anti-CHOPP antibodies
- Thrombogenic markers

Adverse Events

Please see sections 6.1.12.2 Overview of Adverse Events and 6.1.12.4 Nonfatal Serious Adverse Events for AEs data.

Antibodies

No FIX inhibitors were detected in any of the subjects.

Three of 21 subjects tested positive for non-inhibitory FIX antibodies. All were prior to treatment. Two were positive at screening prior to treatment. One tested positive during the PK phase. Subject (b) (6) tested positive at screening and at the 5 ED visit; Subject (b) (6) tested positive at the PK phase; and Subject (b) (6) repeatedly tested positive starting at screening and throughout the study (screening, 5 ED, 12 ED, 25 ED, 50 ED, 75 ED, and end of study). There were no safety or efficacy concerns with these subjects.

Three of 21 subjects developed anti-CHOPP antibodies. Subject (b) (6) tested positive at 25, 50, 100, and 125 ED, and at end of study. Subject (b) (6) tested positive at 50 ED and at end of study. Subject (b) (6) tested positive at end of study. There were no safety or efficacy concerns with these subjects.

There was no correlation between the three subjects who developed anti-CHOPP antibodies and the three subjects who tested positive for non-inhibitory antibodies. There were no apparent safety concerns identified in the subjects who developed these antibodies.

Thrombogenic Markers

The markers of thrombogenicity included prothrombin F1+2, TAT, and D-dimer. These were evaluated with the PK studies pre-infusion at 15 to 30 min post-infusion, 4 to 6 hours post-infusion, and 24 to 26 hours post-infusion. Levels that were above the limit of quantification or below the limit of quantification were excluded from the summary.

The mean prothrombin F1+2 increased from baseline at all timepoints post-infusion. The mean TAT decreased from baseline at 15 to 30 minutes post-infusion and increased from baseline at 4 to 6 hours and 24 to 26 hours post-infusion. Mean D-dimer increased from baseline at all timepoints post-infusion. There was significant variability amongst the results that ultimately didn't reveal any pattern of thrombogenicity with Ixinity.

Reviewer Comment: No safety concerns related to lab values including immunogenicity and thrombogenic markers. No inhibitors detected.

6.1.12.1 Methods

Safety of study subjects was monitored in terms of AEs, immunogenicity, history and physical examination, laboratory measurements, and bleeding assessments. Although bleeding was monitored and considered an efficacy outcome, subjects were monitored for development of

inhibitors that might predispose to bleeding. FIX was assessed pre- and post-PK infusion. Immunogenicity testing by (b) (4) assay, or (b) (4), included non-inhibitory binding FIX antibodies, inhibitory FIX antibodies, and anti-CHOPP antibodies. Inhibitors to FIX antibodies were to be sent at any time if the investigator assessed a sub-optimal response to treatment. Thrombogenicity markers included prothrombin F1+2, TAT, and D-dimer. The protocol included pre-specified definitions of adverse reactions including severity, seriousness, and relatedness. An SMC monitored the study.

6.1.12.2 Overview of Adverse Events

Sixteen subjects were reported to have at least one TEAE. Two subjects had serious TEAEs; 1 subject had a TEAE that was assessed as possibly related to the study drug; and 2 subjects had TEAEs that led to study termination. All non-serious TEAEs were resolved. Overall, the only TEAE that was considered related to the study drug was hypersensitivity and the subject was discontinued from the study due to this TEAE.

Table 9. Overview of Adverse Events, Safety Population

Number of Subjects With ≥1	Age Group <6 Years (n = 10) n (%) E	Age Group 6 to <12 Years (n = 11) n (%) E	Total (N = 21) n (%) E
TEAE ^a	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 ^b	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: APVO101-903 CSR page 91

a. A TEAE is defined as an adverse event that worsens after the first study drug administration.

b. A TEAE is considered drug related if relationship to study drug is missing, “probably related”, “possibly related”, or “definitely related.”

NOTE: Percentages are based on N.

Abbreviations: E, number of events; n (%), count and percentage; N, number of subjects in population; TEAE, treatment-emergent adverse event.

6.1.12.3 Deaths

There were no deaths in the study.

6.1.12.4 Nonfatal Serious Adverse Events

Two serious TEAEs were reported in one subject each. One subject experienced severe hematuria and the other subject experienced a moderate spinal compression fracture. Both events were considered unrelated to Ixinity. The subject who experienced spinal compression permanently discontinued from the study.

6.1.12.5 Adverse Events of Special Interest

Allergic Reactions

One subject had a hypersensitivity reaction that the investigator designated as possibly related to Ixinity. This led to the subject’s permanent discontinuation from the study. There were no reports of anaphylaxis or other significant allergic reactions.

Nephrotic Syndrome

There were no reports of nephrotic syndrome during the study.

FIX Inhibitors

There were no FIX inhibitors found in the subjects during the study.

Thromboembolic Events

There were no thromboembolic events reported during the study.

Reviewer Comment: There were no serious TEAEs related to study product. All were resolved. Two subjects discontinued Ixinity; one due to a non-serious TEAE of hypersensitivity that was related to study products and one non-serious TEAE of spinal compression fracture that was not related to study product.

6.1.12.6 Clinical Test Results

No safety concerns were raised by clinical laboratory results or vital signs. Laboratory results evaluated included complete blood count (CBC) with differential, CD4 count, serum chemistry, and urinalysis. CD4 count was only done at screening. CBC with differential, serum chemistry, and urinalysis were done at screening at 25 ED, 50 ED, 75 ED, 100 ED, then every 3 months, and end of study. For research participants below 17 kg, CBC with differential and serum chemistry were only collected if blood volumes allowed.

Vital signs and physical exams were done at each visit.

6.1.12.7 Dropouts and/or Discontinuations

See 6.1.11.4 Dropouts and/or Discontinuations.

6.1.13 Study Summary and Conclusions

Overall, Ixinity demonstrated efficacy with reduction in ABR with the use of prophylactic Ixinity compared with ABR 6 months prior to enrollment. Efficacy was based on the ABR during prophylactic treatment with Ixinity compared with the ABR during prophylactic treatment with prior product recorded for the same subject. The primary endpoint for this study was met. The ABR with prophylactic Ixinity treatment of 2.34 overall in the treatment and continuation phases was lower than the mean historical rate of 3.5. Ixinity also showed effective treatment of bleeding episodes from both subject/caretaker and investigator ratings. The product was shown to be effective when used for prophylaxis based on investigator rating of preventing bleeding episodes.

While there were no surgeries during this study in subjects <12 years of age, the surgery data from subjects ≥12 years of age from study IB1001-01 who underwent perioperative management with Ixinity had acceptable efficacy outcomes. This includes 3 adolescent pediatric subjects 12, 14, and 16 years of age. Also, it is recommended that dosing perioperatively be calculated based on FIX activity levels. Therefore, the review team feels that extrapolation from the data in subjects ≥12 years of age along with the recommendation to calculate perioperative dosing based on FIX activity levels is adequate for approval for perioperative management indication in subjects <12 years of age.

The safety profile is acceptable and there were no new major safety signals were found.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Not studied.

9.1.2 Use During Lactation

Not studied.

9.1.3 Pediatric Use and PREA Considerations

Please see 5.4 Consultations for further details on pediatric use and PREA considerations. The safety profile is acceptable and there were no new major safety signals were found.

9.1.4 Immunocompromised Subjects

Not studied.

9.1.5 Geriatric Use

Not applicable.

10. CONCLUSIONS

Ixinity is effective in the control and prevention of bleeding, routine prophylaxis, and perioperative prophylaxis in adults and children with hemophilia B. Calculations from Medexus Pharmaceuticals, Inc., were reproduced and confirmed by both the clinical, pharmacology, and statistical reviewers. In 21 pediatric subjects, development of inhibitory antibodies against the product was not observed. No serious TEAEs were found to be related to the study drug.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 10. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> •Hemophilia B is a rare condition with variable deficiency of coagulation FIX. •Hemophilia is accompanied by bleeding into tissues and joints which can be spontaneous, post-traumatic, or perioperative. •Bleeding can be acutely devastating, such as intracranial bleeding, or chronically destructive such as hemophilic arthropathy. 	<ul style="list-style-type: none"> •Hemophilia B is a serious, progressive, life-threatening disease. •The bleeding associated with hemophilia can cause clinically significant complications.
Unmet Medical Need	<ul style="list-style-type: none"> •There are 5 other recombinant FIX products licensed for use by FDA, 2 of which are standard half-life products and 3 of which are extended half-life products. •Several plasma-derived FIX products are approved. However, these approved products carry the risks of infection with known or unknown agents, acute hypersensitivity reactions, or immunogenicity with resistance. 	<ul style="list-style-type: none"> •Increasing the number of available licensed products could have a positive impact and allow options for hemophilia subjects •Ixinity is a recombinant product with less risk of infections, hypersensitivity, or immunogenicity compared to plasma-derived products.
Clinical Benefit	<ul style="list-style-type: none"> •Ixinity was shown to be effective for treatment of, and prevention against spontaneous or traumatic bleeding by both prophylactic or on-demand regimens. •Ixinity was shown to be effective in the perioperative setting for reduction of bleeding during surgery. 	<ul style="list-style-type: none"> •Study XXX demonstrates the effectiveness of Ixinity in pediatric patients XXX of age.
Risk	<ul style="list-style-type: none"> •Three subjects out of 21 developed non-neutralizing antibodies to FIX and 3 subjects had anti-CHOPP antibodies. •No associated clinical sequelae were noted. •The long-term consequences of indeterminate or non-neutralizing FIX antibodies and/or CHOPP antibodies are unknown though cross-reactivity with innate proteins is possible. 	While there remains uncertainty regarding long-term risks following treatment with Ixinity, based on available data and information, the risks appear acceptable for the indicated population.
Risk Management	An approval is recommended.	The risks for the indicated population can be adequately managed through product labeling.

Abbreviations: Anti-CHOPP, anti-Chinese hamster ovary cell proteins; FDA, Food and Drug Administration; FIX, Factor IX; PMC, postmarketing commitment.

11.2 Risk-Benefit Summary and Assessment

A risk assessment analysis was performed and showed no associated clinical findings in study subjects with non-inhibitory antibody formation to FIX and/or CHOPP during the development program for Ixinity including no AEs, lack of therapeutic effect, or alterations in pharmacokinetics. No inhibitory antibodies were detected. There was no thrombosis or pattern of thrombogenicity with Ixinity in patients with out-of-range values for thrombogenic markers.

Due to the effective hemostasis in control and prevention of bleeding episodes, routine prophylaxis and perioperative prophylaxis in adults and children with hemophilia B, the benefits are considered to outweigh the risks of this product.

No new risks were identified in the pediatric trial. No new pharmacovigilance plan or post-marketing risk mitigation management activities were provided nor requested. Overall, the benefit-risk profile is favorable. 11.3 Discussion of Regulatory Options
The regulatory option discussed was approval of the indications of control and prevention of bleeding, routine prophylaxis, and perioperative prophylaxis in children with hemophilia B.

11.4 Recommendations on Regulatory Actions

An approval is recommended.

11.5 Labeling Review and Recommendations

In conjunction with the Advertising & Promotional Labeling Branch (APLB), Clinical Pharmacology Branch, and Nonclinical Branch, a labeling review with recommendations was sent to Medexus Pharmaceuticals, Inc., and negotiated from February 1, 2024. The amended draft package insert submitted on March 22, 2024 is acceptable.