Clinical Pharmacology BLA Review
Office of Clinical Evaluation
Office of Therapeutic Products

BLA	125426/223
Product	IXINITY®, Recombinant Coagulation Factor IX
Applicant	Medexus Pharma, Inc.
Proposed Indication	Treatment of pediatric patients <12 years of age with hemophilia B including on-demand treatment and control of bleeding episodes, perioperative management, and routine prophylaxis to reduce the frequency of bleeding episodes
Date Received	May 22, 2023
Reviewer	Sojeong Yi, Ph.D. Clinical Pharmacology Reviewer, General Medicine Branch 4, Division of Clinical Evaluation General Medicine
RPM	Catherine Tran
Through	Lola Fashoyin-Aje, MD, MPH Director, Office of Clinical Evaluation

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1 EXECUTIVE SUMMARY

IXINITY is a purified recombinant human coagulation factor IX protein, which was initially approved on April 29, 2015, for control and prevention of bleeding episodes, and for peri-operative management of bleeding in adults and children ≥ 12 years of age with hemophilia B. Currently, IXINITY is also indicated for routine prophylaxis to reduce the frequency of bleeding episodes in adults and children ≥ 12 years of age with hemophilia B.

At the initial BLA approval, the following post-marketing requirement (PMR) under the Pediatric Research Equity Act (PREA) was issued:

> Deferred pediatric study IB1001-02 under PREA for the treatment of hemophilia B in pediatric patients ages 0 to 12.

Since June 2021, the current Applicant (Medexus Pharma) has acquired all rights to IXINITY and assumed the clinical development program from (b) (4) . The deferred pediatric Study IB1001-02 was terminated after enrollment of 9 pediatric subjects, and a new pediatric study, Study APVO101-903 was conducted and completed.

In this BLA efficacy supplement, the Applicant submitted the final study report of Study APVO101-903 to request to fulfill the PMR. Additionally, the Applicant proposed to expand the current indication of IXINITY to pediatric patients 0 to 12 years of age based on results of Study APVO101-903. The preliminary data from the terminated Study IB1001-02 was summarized in the submission.

Study APVO101-903 was a single arm, open-label study to evaluate the safety, efficacy, and pharmacokinetics (PK) of IXINITY in 21 subjects < 12 years of age with hemophilia B who had been previously treated (PTPs) with plasma-derived and/or recombinant factor IX products for ≥ 50 exposure days (EDs). The study consisted of three phases, i.e., a PK phase following a single dose of IXINITY, a treatment phase for prophylaxis for at least 50 EDs, and a continuation phase for subjects with ≥ 50 EDs.

This clinical pharmacology review focuses on pharmacokinetics and immunogenicity in Study APVO101-903. The PK analysis was conducted in 20 subjects <12 years of age following a single intravenous (IV) dose of IXINITY 75 (±5) IU/kg in the PK phase. Body weight-adjusted clearance and factor IX incremental recovery in pediatrics < 12 years of age was 33% higher and 20% lower than those in patients ≥12 years of age, respectively. However, the PK parameters were similar between the two pediatric age groups (<6 years vs 6 to <12 years). During the study, none of the 21 subjects who were treated with IXINITY developed FVIII inhibitors. Non-inhibitory factor IX antibodies and antibodies to Chinese hamster ovary cell proteins (CHOP) were detected in 3 subjects each (14.3% each).

The proposed dosing regimens of IXINITY for pediatrics < 12 years are consistent with the doses used in Study APVO101-903, which demonstrated clinical efficacy with a tolerable safety profile. Therefore, the proposed dosing regimen is acceptable. From a clinical pharmacology standpoint, this sBLA of IXINITY is approvable.

2 RECOMMENDATION

The clinical pharmacology information in this sBLA is acceptable to support the approval of IXINITY for use in pediatrics < 12 years of age with hemophilia B, provided that the Applicant and the FDA come to a satisfactory agreement regarding the labeling (see Section 4 for clinical pharmacology labeling comments). Additionally, the PMR is fulfilled from a clinical pharmacology standpoint.

3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Pharmacokinetics of IXINITY in Subjects < 12 years of age

- In Study APVO101-903, pediatric subjects < 12 years of age showed higher body weight-adjusted clearance, lower incremental recovery, and shorter half-life than the previously reported values in subjects ≥ 12 years of age in Study IB1001-01. However, the PK parameters were similar between the two pediatric age groups (<6 years vs 6 to <12 years).
- The mean (±SD) body weight-adjusted clearance in pediatrics < 12 years of age [6.8 ± 1.5 mL/(kg·hr); n=20] was 33% higher by than those in adolescents and adults (≥ 12 years old) [5.1 ± 1.3 mL/(kg·hr); n=32]. The incremental recovery in pediatrics < 12 years of age was 20% lower than subjects ≥ 12 years old [0.79 ± 0.16 (IU/dL)/(IU/kg) vs 0.98 ± 0.21 (IU/dL)/(IU/kg)]. The mean terminal half-life was shorter in pediatrics < 12 years compared to adults and adolescents (16 hours vs 24 hours).
- This finding is consistent with the known PK characteristics of factor IX in pediatrics < 12 years of age compared to adolescents and adults. It supports the dose individualization considering the lower factor IX incremental recovery in patients < 12 years of age.

Proposed Dosing Regimen IXINITY in Subjects < 12 years of age

- For on-demand treatment, control of bleeding episodes, and perioperative management of bleeding, the dose of IXINITY in patients < 12 years of age will be individualized considering the desired peak factor IX increase (in IU/dL) and the mean incremental recovery observed in subjects < 12 years of age evaluated in Study APVO101-903, i.e., 0.79 (IU/dL)/(IU/kg), indicating that 1 IU/kg dose of IXINITY increases the circulating activity of factor IX by 0.79 IU/dL.
- For routine prophylaxis, the recommended dose range is 35 to 75 IU/kg twice weekly for patients < 12 years of age, which is aligned with the average dose (range) of IXINITY evaluated in Study APVO101-903, i.e., 55 IU/kg (32-73) once or twice weekly.

Immunogenicity of IXINITY in Subjects < 12 years of age

- During Study APVO101-903, none of the 21 subjects who were treated with IXINITY developed inhibitory factor IX antibodies.
- Non-inhibitory anti-factor IX antibodies and anti-CHOP antibodies were detected in 3 subjects each (14.3% each). The clinically significant effects of these antibodies on the pharmacokinetics, safety, effectiveness of IXINITY were not identified.

4 CLINICAL PHARMACOLOGY LABELING COMMENTS

The clinical pharmacology reviewer has reviewed the proposed updates on the PI and finds it acceptable pending the final agreement on revisions.

We have recommended the following revisions to the Applicant's proposed updates:

- In Section 8.4. Pediatric Use, delete the detailed results of Study APVO101-903 that are also described in Sections 12.3, 12.6., and 14 to avoid redundancy, consistent with to FDA guidance - *Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling* (March 2019).
- In Section 12.3. Pharmacokinetics, use the consistent units of volume of distribution and clearance between PTPs < 12 years of age and ≥ 12 years of age.
- Re-organize the immunogenicity information according to FDA guidance for industry – *Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling- Content and Format* (draft, Feb 2022) and move it to Section 12.6 Immunogenicity from Section 6.2.
- Describe immunogenicity of subjects < 12 years of age separately from those of subjects ≥ 12 years of age under Section 12.6. Immunogenicity

5 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

Study APVO101-903 was a single arm, open-label study to evaluate the safety, efficacy, and PK of IXINITY in subjects < 12 years of age with hemophilia B who had been previously treated with factor IX products for a minimum of 50 EDs. The study consisted of three phases, i.e., a PK phase following a single dose of IXINITY, a treatment phase for prophylaxis for at least 50 EDs, and a continuation phase for subjects with ≥ 50 ED. A total 21 subjects received IXINITY for routine prophylaxis and control of bleeding episodes. Although subjects were allowed to use IXINITY for peri-operative management if required, none of the subjects received surgery and used IXINITY for peri-operative management during the trial.

Of note, a summary of the data deriving from the terminated pediatric study, Study IB1001-02, was provided in the submission; the final report is pending.

See Appendix for further details of Study APVO101-903 and the data summary of Study IB1001-02 from 9 enrolled subjects.

5.1 Pharmacokinetics of IXINITY in Subjects < 12 Years of Age

The PK assessment was conducted in the PK phase of Study APVO101-903 following a single IV infusion of IXINITY 75 (±5) IU/kg, which was preceded by a washout period of 4 days or a period of 3 half-lives washout of previous factor IX products with a prolonged half-life.

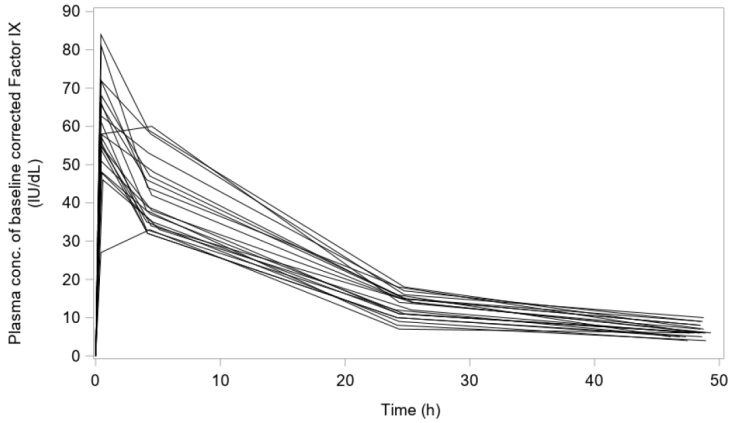
Plasma concentration of factor IX was assessed at pre-infusion and up to 50 hours post-infusion (at 0.25 -0.5 hours, 4-6 hours, 24-26 hours, and 46-50 hours). In each subject, pre-infusion

concentration was subtracted from post-infusion concentrations (i.e., baseline correction) and all negative baseline-corrected concentrations were set to zero to estimate PK parameters.

Out of a total 21 subjects who participated in the PK phase, 20 subjects (n=10, < 6 years of age; n=10, 6 to <12 years of age) were included in PK analysis because one subject who received a lower dose of 66 IU/kg than the planned dose of 75 (±5) IU/kg was excluded from PK analysis.

Individual baseline-corrected plasma factor IX concentration-time profiles are presented in Figure 1. The maximum factor IX concentration was reached within 0.5 hours post-infusion, and after which the concentration gradually declined.

Figure 1. Individual Baseline-Corrected Plasma Factor IX Concentration-Time Profiles of After Single IV Infusion of IXINITY 75 ± 5 IU/kg



Source: Study APVO101-903 Pharmacokinetics Report, Figure 3

Table 1 presents PK parameters of IXINITY in 20 subjects <12 years of age compared to those of 32 subjects ≥12 years of age in Study IB1001-01. Subjects < 12 years of age showed 33% higher body weight-adjusted clearance and 20% lower incremental recovery compared to subjects ≥ 12 years of age. The mean terminal half-life was shorter in pediatrics < 12 years compared to adults and adolescents, i.e., 16 hours vs 24 hours. However, the PK parameters were similar between two younger age groups, <6 years vs 6 to <12 years.

A lower incremental recovery and a higher clearance in pediatrics ≤12 years of age compared to adults and adolescents is known PK characteristics of factor IX protein[1,2]. It supports the need of dose individualization considering factor IX incremental recovery by age group (≥ 12 years of age vs < 12 years of age).

[1] Poon MC et al. Recombinant factor IX recovery and inhibitor safety: a Canadian post licensure surveillance study. Thromb Hemost 2002; 87:431–435.
[2] Nagel, K et al. Pharmacokinetics of recombinant and plasma-derived factor IX products in pediatric patients with severe hemophilia B. Blood Coagulation & Fibrinolysis 2015; 26(1): 113-114

Table 1. Pharmacokinetic Parameters of IXINITY in Subjects <12 Years of Age (Study APVO101-903) and Subjects ≥12 Years of Age (Study IB1001-01) After Single IV Infusion of IXINITY 75 ± 5 IU/kg

Parameters Mean ± SD (Min, Max)	Age <6 years (N=10)	Age 6 to <12 years (N=10)	Age <12 years (N=20)	Age ≥12 years (N=32) (Study IB1001-01)
N	10[a]	10[b]	20[c]	32
C_{max} (IU/dL)	56.4 ± 13.7 (33, 84)	63.7 ± 9.86 (48, 81)	60.1 ± 12.2 (33, 84)	73.2 ± 16.6 (51, 113)
$AUC_{0-\infty}$ (IU/dL/hr)	1118 ± 307 (853, 1528)	1232 ± 81.7 (1129, 1308)	1170 ± 231 (853, 1528)	1573 ± 451 (862, 2643)
AUC_{0-t} (IU/dL/hr)	909 ± 227 (677, 1381)	1098 ± 137 (871, 1339)	1003 ± 207 (677, 1381)	1375 ± 356 (821, 2172)
Mean Residence Time (hr)	19.9 ± 2.48 (16.5, 22.8)	20.0 ± 2.87 (16.3, 23.8)	20.0 ± 2.53 (16.3, 23.8)	31.9 ± 6.38 (18.9, 46.6)
Terminal Half-life (hr)	15.9 ± 1.4 (14.0, 17.5)	16.8 ± 2.8 (13.1, 21.2)	16.3 ± 2.2 (13.1, 21.2)	24.2 ± 6.9 (13.3, 43.0)
Clearance [mL/(kg·hr)]	7.28 ± 1.87 (4.91, 9.03)	6.13 ± 0.507 (5.66, 6.82)	6.76 ± 1.49 (4.91, 9.03)	5.1 ± 1.3 (2.8, 7.7)
Vd_{ss} (mL/kg)	144 ± 36.7 (87.7, 179)	123 ± 18.9 (106, 147)	134 ± 30.6 (87.7, 179)	175 ± 57 (102, 314)
Incremental Recovery [(IU/dL)/(IU/kg)]	0.731 ± 0.149 (0.440, 0.966)	0.849 ± 0.147 (0.608, 1.09)	0.790 ± 0.156 (0.440, 1.09)	0.98 ± 0.21 (0.67, 1.50)
In Vivo Recovery	0.329 ± 0.0671 (0.198, 0.434)	0.382 ± 0.0666 (0.273, 0.492)	0.355 ± 0.0705 (0.198, 0.492)	0.44 ± 0.09 (0.30, 0.68)

a. n=6 for $AUC_{0-\infty}$, mean residence time, terminal half-life, clearance, and Vd_{ss}.
b. n=6 for terminal half-life and n=5 for $AUC_{0-\infty}$, mean residence time, clearance, and Vd_{ss}.
c. n=12 for terminal half-life and n=11 for $AUC_{0-\infty}$, mean residence time, clearance, and Vd_{ss}.

Abbreviations: Cmax, maximum concentration; AUC, area under the curve; Vd_{ss}, volume of distribution at steady state
Source: Study APVO101-903 Pharmacokinetics Report, Table 14.2.07; Study IB1001-01 Study Report, Section 11.4.1.1.1

5.2 Recommended Dosing Regimen of IXINITY in Subjects < 12 Years of Age

Dosage and duration of treatment for IXINITY should be individualized based on the severity of the factor IX deficiency, the location and extent of bleeding, the patient's clinical condition, age, and pharmacokinetic parameters of factor IX, such as incremental recovery and half-life.

Initial dose

The initial dose of IXINITY (IU) is calculated as follows: 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). For adolescents/adults (≥ 12 years of age), the incremental recovery of 0.98 IU/dL per IU/kg has been used to determine the initial dose. For children < 12 years of age, the Applicant proposed to use the incremental recovery of 0.79 (IU/dL)/(IU/kg) based on the mean incremental recovery observed in subjects < 12 years of age in Study APVO101-903, which is acceptable.

On-demand treatment, control of bleeding episodes, and perioperative management of bleeding

The current dosing guides of IXINITY for patients ≥ 12 years of age in terms of desired factor IX level, dosing interval, and duration of treatment will be applied consistently to patients < 12 years, which is aligned with the clinical guideline[3] and other approved factor IX products approved (e.g., BENEFIX, RIXUBIS).

The dose will be determined according to individual patient's incremental recovery. For patients ≥ 12 years of age, 1 IU/kg of IXINITY increases the circulating activity of factor IX by 0.98 IU/dL. However, for patients < 12 years of age, the mean incremental recovery observed in APVO101-903 indicates that 1 IU/kg of IXINITY increases the circulating activity of factor IX by 0.79 IU/dL.

Routine prophylaxis

For PTPs ≥ 12 years of age, the recommended dose of IXINITY has been 40 to 70 IU/kg twice weekly. For PTPs < 12 years of age, the Applicant proposed to recommend 35 to 75 IU/kg twice weekly.

In Study APVO101-903, the recommended prophylaxis dose range of IXINITY was 35 to 75 (± 5) IU/kg once or twice weekly based on the approved prophylaxis dose in PTPs ≥ 12 years of age and the clinical guideline[3] recommending 40-60 IU/kg twice weekly for high dose prophylaxis with standard half-life clotting factor. As a result, the mean (range) doses used in subjects < 6 years old and subjects 6 to < 12 years old were 58 (45-72) IU/kg and 52 (46-60) IU/kg, respectively. Most patients administered IXINITY twice weekly.

As the proposed prophylaxis regimen is consistent with the dose evaluated in Study APVO101-903 showing adequate efficacy and safety, it is acceptable.

5.3 Immunogenicity of IXINITY in Subjects < 12 Years of Age

In all 21 subjects in Study APVO101-903 were monitored for inhibitory and non-inhibitory antibodies to factor IX and anti-CHOP antibodies at pre-infusion of the PK phase, 5, 12, 25, 50, 75, 100 EDs, and every 3 months thereafter of the treatment/continuation phases.

Factor IX inhibitor titer ≥ 0.6 Bethesda Unit was determined as inhibitor positive and none of 21 subjects developed inhibitory factor IX antibodies, including 19 subjects with > 50 EDs and 16 of those subjects with > 100 EDs.

[3] Srivastava A, et al. World Federation of Hemophilia guidelines for the management of hemophilia. 3rd Edition, Haemophilia. 2020; 26 (Supple 6): 1-158

Non-inhibitory anti-factor IX antibodies were developed in 3 of 21 subjects (14.3%). In one of the subjects, the non-inhibitory factor IX antibodies were persistent throughout the study whereas in the other two subjects, the presence of antibodies were transient.

Anti-CHOP antibodies were developed in 3 of 21 subjects (14.3%), which were sporadic and non-persistent in two subjects but in one subject, the anti-CHOP antibodies were persistent.

There was no correlation between the 3 subjects with non-inhibitory factor IX antibodies and the 3 subjects with anti-CHOP antibodies.

Of note, in previous clinical studies of IXINITY in subjects ≥ 12 years of age, none of subjects developed factor IX inhibitor and 30% (23/77) and 29% (20/68) of subjects developed non-inhibitory anti-factor IX antibodies and anti-CHOP antibodies, respectively. Overall, the observed incidence rates of anti-drug antibodies in subjects < 12 years of age were relatively lower than those of patients > 12 years of age.

No clinically significant effects of these antibodies on the pharmacokinetics, safety, effectiveness of IXINITY have been identified.

6 APPENDIX - INDIVIDUAL STUDIES

Study APVO101-903

Title: Evaluation of a recombinant factor IX product, APVO101, in previously treated pediatric patients with hemophilia B

Objectives:

- To evaluate the safety of APVO101 in pediatric subjects with hemophilia B for at least 50 ED.
- To assess the efficacy of APVO101 prophylaxis with respect to prevention of breakthrough bleeding and with respect to control of hemorrhaging in pediatric subjects with hemophilia B for at least 50 ED.
- To evaluate the PK of APVO101 in pediatric subjects with hemophilia B.
- To evaluate APVO101 immunogenicity response (development of inhibitory and non-inhibitory factor IX binding antibodies and antibodies to CHOP)

Methodology: Study APVO101-903 was a single-arm, open-label clinical study. The study was designed to gather information in 2 age groups of previously treated (with a minimum of 50 previous exposure days (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 – after completion of the PK Phase, subjects received APVO101 prophylaxis (starting prophylaxis dose was to be determined based on APVO101 recovery; ideally within the recommended dose range: 35-75 IU/kg, twice weekly) for 50 ED (approximately 6 months).
- Continuation Phase – subjects continued to receive APVO101 prophylaxis (recommended dose range: 35-75 IU/kg, twice weekly) for an additional ≥50 ED.

The PK evaluation was preceded by a washout period of 4 days or a period of 3 half-lives washout of a factor IX product with a prolonged half-life, followed by PK and safety assessments to be completed within 50 hours after APVO101 infusion.
The Treatment Phase included a minimum of 6 months of APVO101 prophylaxis to obtain 50 ED, and the Continuation Phase included APVO101 prophylaxis for an additional ≥50 ED (≥6 months). Between 15 and 20 evaluable subjects were planned to complete all phases of the study. Treatment with APVO101 to support a surgical procedure was permitted for subjects in the Treatment/Continuation phases of the study if required. The duration of subject study participation could vary depending on the time of enrollment into the study but was to be for at least 12 months.

Subject Disposition: Up to 22 subjects were to be enrolled in the study in order to have 15 to 20 evaluable subjects complete a minimum of 50 ED. There were 10 subjects in the <6 years group and 11 subjects in the 6 to <12 years group. A total of 21 subjects were enrolled in the study.
A total 19 subjects completed 50 ED visits and proceeded to the Continuation Phase, and 2 subjects discontinued from the Treatment Phase (1 subject due to an adverse event and 1 subject due to voluntary withdrawal). None of them needed to be treated with APVO101 for peri-operative management.
Of 19 subjects who entered the Continuation Phase, 4 subjects had >50 ED visits but <100 ED visits; 15 subjects had ≥100 ED visits; 14 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.
Number of subjects that were included clinical evaluations as follows:

- Safety analysis set: all 21 subjects.
- Efficacy analysis set: all 21 subjects (including 1 subject who discontinued after 13 ED)
- PK analysis set: 20 subjects excluding 1 subject (ID: (b) (6)) who received a lower dose of 66 IU/kg in the PK phase, instead of the 75 (±5) IU/kg that was originally planned in the study protocol.

Investigational Product: APVO101 (the marketed name, IXINITY) in single-use glass vials containing nominally 250, 500, 1000, 1500, 2000, or 3000 IU of recombinant coagulation factor IX, lyophilized for intravenous administration after reconstitution. The recommended infusion rate was 10 mL/min.
Dosage Administration:

1) PK Phase: a single IV dose of 75 (±5) IU/kg
2) Treatment Phase/Continuation Phase

- Prophylaxis: 35-75 IU/kg twice weekly or at a frequency per investigators' discretion

- Minor/moderate bleeding episodes: 40-60 IU/kg (single dose)
- Major/life-threatening bleeding episodes: 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.

Pharmacokinetic Assessment:

Plasma factor IX activity was assessed at pre-infusion and up to 50 hours post-infusion (at 15-30 minutes, 4-6 hours, 24-26 hours, and 46-50 hours post-infusion) following a single dose of 75 (±5) IU/kg in the PK phase. Plasma concentrations of factor IX were determined using a clotting factor assay with a lower limit of quantification (LLOQ) of 1 IU/dL. For baseline correction, in each individual subject, pre-infusion concentration was subtracted from post-infusion concentrations. All negative baseline-corrected concentrations were set to zero to estimate PK parameters.

A total 20 subjects were included in PK analysis excluding one subject due to protocol deviation as follows:

• Subject (b) (6) received a dose of 66 IU/kg instead of the planned dose of 75 (±5) IU/kg.

See Section 5.1 for the details of pharmacokinetic results.

Immunogenicity Assessment:

Factor IX Inhibitor titer, non-inhibitory factor IX binding antibodies, and anti-CHOP antibodies were assessed at screening, pre-infusion of the PK phase, 5, 12, 25, 50, 75, 100 EDs, and every 3 months until the End of Trial (EOT), EOT during the Treatment/Continuation phases.

Inhibitory factor IX antibodies were analyzed by both Bethesda assay and Nijmegen modified Bethesda assay at screening, and by Nijmegen modified Bethesda assay thereafter. Factor IX inhibitor < 0.6 Bethesda Unit was determined as negative. Non-inhibitory factor IX binding antibodies and anti-CHOP antibodies were analyzed by (b) (4).

See Section 5.3 for the details of immunogenicity results.

Efficacy/Safety Assessment Conclusion:

The primary efficacy endpoint was annualized bleeding rate (ABR) while on prophylaxis to prevent bleeding episodes. The mean ABRs (95% CI) and the mean spontaneous ABRs (SABR) for the overall period (the Treatment Phase and the Continuation Phase) were as follows by age group:

- ABR: 2.34 (1.8-3.1) for all subjects < 12 years of age; 3.60 (2.6-5.0) in the <6 years of age group; 1.19 (0.7;2.0) in the 6 to <12 years of age group
- SABR: 0.63 (0.4;1.1) for all subjects < 12 years of age; 0.55 (0.2-1.3) in the <6 years of age group; 0.70 (0.3;1.4) in the 6 to <12 years of age group

The secondary efficacy endpoints were about bleeding episodes. For all 21 subjects, 52 bleeding episodes occurred for all 21 subjects (28 in the <6 years of age group; 24 in the 6 to <12 years of age group). No subjects underwent surgical procedures during the reported study period.

The safety assessment based on clinical laboratory parameters, vital signs, physical exams, and adverse events indicated a favorable safety profile at a mean average dose per ED of 1539.7 IU (54.81 IU/kg) treated for a mean 159 EDs.

In conclusion, APVO101 was generally safe and effective in the prophylactic treatment and the control and management of bleeding episodes for pediatric subjects < 12 years of age with moderate to severe hemophilia B. However, the adequacy of the Applicant's efficacy and safety assessments is deferred to the clinical reviewers. Please refer to the clinical review memo on BLA 125426/223.

Source: Study APVO101-903 Clinical Study Report

Summary of Study IB1001-02 (Terminated)

Objectives: To evaluate PK, safety, and efficacy were evaluated in PTPs <12 years old with severe or moderately severe hemophilia B (factor IX activity ≤2%).

Number of Subjects:
A total of 9 subjects (3 subjects <6 years and 6 subjects 6-12 years) were enrolled in the study prior to termination. All were prescribed a prophylaxis regimen following PK assessment; 1 subject erroneously received on-demand treatment. PK analysis was performed for 6 subjects.

Efficacy: The median ED for subjects on prophylaxis was 221 days (range 111-404) and the median time between first and last treatment was 46 months. The median total number of bleeds per subject was 1 (range 0-6); 2 subjects experienced no bleeds. The median ABR was 0.3 bleeding episodes per year (range 0-1.6). The subject who received on-demand treatment experienced 23 bleeds with an ABR of 11.

Safety: No adverse events related to APVO101 were reported.

Pharmacokinetics: Following a minimum 4-day washout of factor IX product, a pre-infusion blood sample was collected to measure factor IX and inhibitor levels. A single intravenous dose of 75 IU/kg APVO101 was administered, with factor IX measurements performed at four time points post-infusion (15-30 min, 4-6, 24-26 and 68-72 hours). If possible, effort was made to collect six time points, with two additional time points at 1-3- and 10-14-hours post-infusion.

The results of the PK analyses are summarized in Table 3. Following a single dose 75 IU/kg, AUC was lower, incremental recovery was lower, and half-life was shorter compared to those of adults and adolescents (≥ 12 years old). This is consistent with the PK pattern of factor IX in pediatrics < 12 years of age when compared to use in adolescents and adults.

Table 2. Pharmacokinetic Parameters of APVO101 from Study IB1001-02

Parameter		APVO101 N=6
$AUC_{0-\infty}$ (IU/hr/dL)	mean ± SD	1062 ± 322
Incremental Recovery (IU/dL per IU/kg)	mean ± SD	0.84 ± 0.50
Terminal half-life (hr)	mean ± SD	22.6 ± 7.0
C_{max} (IU/dL)	mean ± SD	51.7 ± 15.7
VDss (mL/kg)	mean ± SD	244 ± 16.6
Clearance ([mL/(kg*hr)])	mean ± SD	7.3 ± 3.1

Source: 2.7.2. Summary of Clinical Pharmacology Studies, Table 7

Immunogenicity: None of the subjects developed inhibitory factor IX antibodies during the study.
During the study, 3 patients developed anti-CHOP antibodies (with no apparent effect on safety or efficacy of APVO101), while 6 patients were anti-CHOP negative.

Source: 2.5. Clinical Overview, 2.7.2. Summary of Clinical Pharmacology Studies, Study APVO101-903 Clinical Study Report