Protocol APVO101-903

Evaluation of a Recombinant Factor IX Product, APVO101, in Previously-Treated Pediatric Patients with Hemophilia B

Version 3.0
Amendment 2 Date: 29 July 2020

Trial Sponsor:	Medexus Pharma, Inc. d.b.a. Aptevo BioTherapeutics, LLC
Medical Monitor:	[redacted]
Study Manager:	[redacted]

Confidentiality Statement

PROTOCOL SIGNATURE PAGE

APVO101-903, Version 3.0, Amendment 2:

Evaluation of a Recombinant Factor IX Product, APVO101, in Previously-Treated Pediatric Patients with Hemophilia B

Clinical Site(s):

My signature below verifies that I have read and agree to this protocol. I am aware of my responsibilities as an Investigator under the GCP guidelines of ICH, the Declaration of Helsinki, local regulations (as applicable) and the study protocol, and I agree to conduct the study according to these regulations.

Site Principal Investigator:

Principal Investigator Name (print)	Title (print)
Principal Investigator Signature	Date (DD/MMM/YYYY)

PROTOCOL SYNOPSIS

Title	**Evaluation of a Recombinant Factor IX Product, APVO101, in Previously-Treated Pediatric Patients with Hemophilia B**
Sponsor	Medexus Pharma, Inc. d.b.a Aptevo BioTherapeutics, LLC 29 N Wacker Drive, Suite 704 Chicago, IL 60606, USA
Trial Start	Anticipated enrollment of first subject: Q3 2019
Objectives	**Primary Objectives** • To evaluate safety of APVO101 in pediatric subjects with hemophilia B for at least 50 exposure days (ED) • To assess efficacy of APVO101 prophylaxis with respect to prevention of breakthrough bleeding and with respect to control of hemorrhaging in pediatric subjects with hemophilia B for at least 50 ED • To evaluate pharmacokinetics (PK) of APVO101 in pediatric subjects with hemophilia B • To evaluate APVO101 immunogenicity (development of inhibitory and non-inhibitory factor IX binding antibodies and antibodies to Chinese Hamster Ovary cell proteins [CHOP]) **Exploratory Objectives** • To evaluate markers of thrombogenicity [D-dimer, thrombin-antithrombin III complex (TAT) and fragment 1+2 (F1+2)] during the first 24 hours post-infusion of APVO101 • To evaluate efficacy of APVO101 for perioperative management in pediatric subjects with hemophilia B
Subject Population	Pediatric patients (< 11.5 years of age at first dose) with hemophilia B that have been previously treated with factor IX replacement therapy for ≥ 50 ED.
Sample Size	Up to 22 subjects will be enrolled in order to have 15 to 20 evaluable subjects (10 subjects < 6 years and 10 subjects 6 to < 12 years) complete the study (i.e., completion of PK assessments and a minimum of 50 ED).
Number of Trial Sites	Study APVO101-903 is a multi-center trial with international investigational sites; exact locations and number of the sites are to be determined.
Test Product	APVO101, a lyophilized coagulation factor IX (recombinant) for intravenous administration.
Dosage	PK Phase dose: a single infusion of 75 ± 5 IU/kg Treatment/Continuation Phase dose: a single infusion of APVO101 twice weekly or at a frequency determined appropriate by the investigator

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	(prophylaxis). The starting prophylaxis dose for but not limited to Treatment Phase will be based on APVO101 recovery; ideally within the recommended dose range of 35 – 75 IU/kg. Dose range for treatment of breakthrough, spontaneous or trauma-related bleeding episodes based on severity: • Minor or moderate bleeds: 40 – 60 IU/kg • Major or life-threatening bleeds: 60 – 100 IU/kg Dose for surgery: • Bolus infusion: up to 120 IU/kg within 1 hour prior to the start of the procedure, followed by an infusion of 60 IU/kg 12 hours after the first infusion and an infusion of up to 120 IU/kg 24 hours after the first infusion. Continue bolus infusions every 12 hours for a minimum of 3 days post-procedure for major surgery or a minimum of 1 day post-procedure for minor surgery. The dosage and frequency of treatment may be adjusted at the discretion of the investigator. • Continuous infusion: target plasma level of factor IX between 70% and 110% for a minimum of 3 days post- procedure for major surgery or a minimum of 1 day post-procedure for minor surgery.
Protocol Design	Phase 3/4, single arm, open-label study with three defined phases: **PK Phase** Initial PK evaluation – single dose of APVO101 **Treatment Phase** APVO101 prophylaxis treatment for 50 ED **Continuation Phase** After completion of the Treatment Phase, subjects may continue APVO101 prophylaxis treatment (for an additional ≥ 50 ED) *Note: treatment with APVO101 to support a surgical procedure (if required) is permitted for subjects in Treatment Phase or Continuation Phase of the study.*
Inclusion Criteria	1. Age: < 11.5 years of age at the time of the first dose and < 12 years throughout the Treatment Phase of the study (for at least 50 ED). 2. Informed consent: subject's parent or legal guardian written Institutional Review Board (IRB)/Ethics Committee (EC)-approved informed consent. An assent form (IRB/EC-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 ED; approximately 6 months).

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	4. Documented severe or moderately severe hemophilia B diagnosis (factor IX 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 factor IX. 5. Subjects must be on prophylaxis or switch to a prophylaxis regimen for the duration of the study. 6. Previously treated patients with a minimum of 50 ED (as documented/determined by the investigator) to a preparation/blood components containing factor IX. 7. Willingness to adhere to the 4-day washout period of any factor IX replacement therapy prior to PK evaluation. In case of previous exposure to a factor IX product with a prolonged half-life, a washout period of 3 half-lives is required in order to achieve steady state factor IX level prior to exposure to APVO101. 8. Immunocompetent (CD4 count > 400/mm^3) and not receiving immune modulating or chemotherapeutic agents. 9. Platelet count at least 150,000/mm^3. 10. Liver function: alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 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 factor IX inhibitor ≥ 0.6 Bethesda Units (BU); confirmed by the screening result. 2. Existence of another coagulation disorder. 3. Evidence of thrombotic disease, fibrinolysis, or disseminated intravascular coagulation (DIC). 4. Use of an investigational drug within 30 days prior to study entry. 5. Previous use of APVO101. 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.

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	10. History of adverse reaction to either plasma-derived factor IX or recombinant factor IX that interfered with the subject's ability to treat bleeding episodes with a factor IX product. 11. History of any medical condition that would impact the efficacy evaluation and/or safety evaluation of the study product.
Assessments	**Screening Assessments (21 to 5 days prior to PK Phase)** Signed and dated Informed Consent Form (ICF) and/or assent form as applicable. Inclusion/exclusion criteria review. Medical and hemophilia-related history, including documentation of factor IX gene mutation, bleeding episode(s), documentation of PK data (e.g., recovery and half-life) utilizing prior non-study factor IX therapy, and documentation of at least 50 ED of factor IX replacement therapy Concomitant medications Demographics (age, sex), body weight, height, physical exam and vital signs Local laboratory assessments: • Serum chemistry [ALT, AST, alkaline phosphatase (ALP), blood urea nitrogen (BUN) or urea, uric acid, creatinine, total bilirubin, and glucose] • Complete blood count (CBC) with differential [hemoglobin, hematocrit, absolute counts and/or percent of: white blood cells, neutrophils, monocytes, lymphocytes, eosinophils, basophils, platelets, and red blood cells; mean platelet volume (MPV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC)] • CD4 count • Urinalysis [urine dipstick, followed by microscopy if abnormal] Central laboratory assessments: • Inhibitory factor IX antibodies (Nijmegen modified Bethesda assay) • Non-inhibitory factor IX binding antibodies • Anti-CHOP antibodies Review of subject diary of previous factor IX therapy (if available): infusions, bleeding summary, subject's efficacy assessment, adverse events, and concomitant medications Investigator's assessment of efficacy with previous factor IX therapy Assessment of major and target joint(s)

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	Assessment of adverse events Review of study requirements, subject diary instructions, and training on APVO101 reconstitution and administration **PK Phase Assessments** After a 4-day washout of factor IX replacement therapy or 3-half-lives washout of a factor IX product with a prolonged half-life, the following will be evaluated: ***Pre-infusion*** Physical exam, vital signs, body weight, height, and concomitant medications, updated medical history (if applicable) Central laboratory assessments: • Inhibitory factor IX antibodies (Nijmegen modified Bethesda assay: for subjects weighing > 28 kg) • Non-inhibitory factor IX binding antibodies (for subjects weighing > 28 kg) • Anti-CHOP antibodies (for subjects weighing > 28 kg) • Factor IX activity • Thrombogenicity markers (see Table 2 for thrombogenicity assessments by subject weight) ***Post-infusion period*** Central laboratory assessments: • Factor IX activity at the following time points post-infusion: 15-30 minutes, 4-6 hours, 24-26 hours and 46-50 hours • Thrombogenicity markers at 15-30 minutes, 4-6 hours and 24-26 hours post-infusion (see Table 2 for thrombogenicity assessments by subject weight) Vital signs at each PK time-point post-infusion Assessment of adverse events *Note: pre-infusion and 15-30 minute post-infusion samples will be tested for factor IX activity to determine starting prophylaxis dose. See section 5.7.1 for further details.* **Treatment Phase Assessments** After the start of APVO101 prophylaxis treatment regimen the following assessments will be performed at: ***5 ED (± 1 ED) and 12 ED (± 2 ED)*** Central laboratory assessments: • Inhibitory factor IX antibodies (Nijmegen modified Bethesda assay)

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	• Non-inhibitory factor IX antibodies • Anti-CHOP antibodies • Mutation genotyping (12 ED visit only, if not documented); for patients below 10 kg this may be done at any time during the study when blood volumes allow Review of subject diary: infusions, bleeding summary, subject's efficacy assessment, adverse events, concomitant medications and compliance Concomitant medications Assessment of adverse events Investigator's assessment of efficacy ***25 ED (± 3 ED) and 50 ED (± 5 ED)*** Physical exam, vital signs, body weight, and height Concomitant medications Local laboratory assessments: • Serum chemistry (for patients below 17 kg, collect if blood volumes allow) • Complete blood count (CBC) with differential (for patients below 17 kg, collect if blood volumes allow) • Urinalysis [urine dipstick, followed by microscopy if abnormal] Central laboratory assessments: • Inhibitory factor IX antibodies (Nijmegen modified Bethesda assay) • Non-inhibitory factor IX binding antibodies • Anti-CHOP antibodies Review of subject diary: infusions, bleeding summary, subject's efficacy assessment, adverse events, concomitant medications, and compliance Assessment of adverse events Investigator's assessment of efficacy Assessment of major and target joints (50 ED only) **Continuation Phase Assessments:** After completion of the Treatment Phase (i.e., 50 ED), subjects may continue with APVO101 treatment in a Continuation Phase (for an additional ≥ 50 ED). The following assessments in the Continuation Phase will be made at 75 ED (±5 ED), 100 ED (±5 ED) and every 3 months (~25 ED ± 5 ED) thereafter until end of study: Physical exam, vital signs, body weight, and height Concomitant medications

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	Local laboratory assessments: • Serum chemistry (for patients below 17 kg, collect if blood volumes allow) • Complete blood count (CBC) with differential (for patients below 17 kg, collect if blood volumes allow) • Urinalysis [urine dipstick, followed by microscopy if abnormal] Central laboratory assessments: • Inhibitory factor IX antibodies (Nijmegen modified Bethesda assay) • Non-inhibitory factor IX binding antibodies • Anti-CHOP antibodies Review of subject diary: infusions, bleeding summary, subject's efficacy assessment, adverse events, concomitant medications, and compliance Assessment of adverse events Investigator's assessment of efficacy Assessment of major and target joints (100 ED visit only) **Surgery Assessments (if applicable)** ***Prior to surgery; pre-infusion*** Documentation of planned surgery including rationale Local laboratory assessment: Factor IX activity Central laboratory assessments: • Factor IX activity (if blood volumes allow) Vital signs Surgeon's assessment of expected/estimated blood loss for the surgical procedure ***Prior to surgery; 5 – 30 minutes post-infusion (bolus)*** Local laboratory assessment: • Factor IX activity Central laboratory assessment: • Factor IX activity (if blood volumes allow) Assessment of adverse events ***During surgery*** Surgeon's assessment of blood loss If study product is infused during surgery, local laboratory assessment: • Factor IX activity pre- and post-infusion (5-30 minutes)

Title	Evaluation of a Recombinant Factor IX Product, APVO101, in Previously-Treated Pediatric Patients with Hemophilia B
	Assessment of adverse events Use of blood products ***End of surgery*** Surgeon's assessment of total blood loss for the surgical procedure Assessment of adverse events Use of blood products Post-surgery ***12 hours (±2 hours) post-initial infusion; pre-infusion*** Local laboratory assessment: • Factor IX activity Central laboratory assessment: • Factor IX activity (if blood volumes allow) Vital signs Surgeon's assessment of blood loss Use of blood products ***12 hours post-initial infusion (±2 hours); 5 – 30 minutes post-infusion (bolus)*** Local laboratory assessment: • Factor IX activity Central laboratory assessment: • Factor IX activity (if blood volumes allow) Assessment of adverse events ***24 hours post-initial infusion (±3 hours); pre-infusion*** Local laboratory assessment: • Factor IX activity Central laboratory assessment: • Factor IX activity (if blood volumes allow) Vital signs Surgeon's assessment of blood loss Use of blood products ***24 hours post-initial infusion (±3 hours); 5 – 30 minutes post- infusion (bolus)*** Local laboratory assessment: • Factor IX activity Central laboratory assessment:

Title	Evaluation of a Recombinant Factor IX Product, APVO101, in Previously-Treated Pediatric Patients with Hemophilia B
	• Factor IX activity (if blood volumes allow) Assessment of adverse events Factor IX activity (local laboratory assessment) should be monitored every 12 hours (±2 hours) thereafter (for a minimum of 3 days post-surgery or until healing in case of a major surgery for major surgery or a minimum of 1 day post-procedure for minor surgery). Factor IX activity should be assessed before and within 30 minutes post-infusion of study product. If blood volumes allow, Factor IX activity should also be assessed by central laboratory at each timepoint. Adjustments in APVO101 dosing and timing post-surgery of each adjustment should be documented. Adverse events should be assessed for the duration of each continuous infusion period (±2 hours). In case of a major surgery (supported by bolus or continuous infusions), surgeon's assessment of blood loss should be performed every 12 hours (±2 hours) for at least 3 days post-surgery or until healing (if applicable). For continuous infusions, factor IX activity (local laboratory assessment), assessment of vital signs and use of blood products (pre-infusion) should be performed at 12-hour (±2 hours) and 24-hour (±3 hours) time points post-surgery and subsequently on a daily basis or more frequently if needed until continuous infusion is discontinued. If blood volumes allow, Factor IX activity should also be assessed by central laboratory at each timepoint. Adjustments in APVO101 dosing and timing post-surgery of each adjustment should be documented. ***28 days (±7 days) post-factor IX replacement therapy for surgery*** Use of blood products **End of Study or Early Withdrawal Assessments** At the end of the study, or for subjects who prematurely terminate or who are withdrawn before the study is complete, the following will be evaluated: Physical exam, vital signs, body weight, height, and concomitant medications Assessment of adverse events Local laboratory assessments: • Serum chemistry (for patients below 17 kg, collect if blood volumes allow) • CBC with differential (for patients below 17 kg, collect if blood volumes allow) • Urinalysis [urine dipstick, followed by microscopy if abnormal] Central laboratory assessments: • Inhibitory factor IX antibodies (Nijmegen modified Bethesda assay) • Non-inhibitory factor IX binding antibodies

Title	**Evaluation of a Recombinant Factor IX Product, APVO101, in Previously-Treated Pediatric Patients with Hemophilia B**
	• Anti-CHOP antibodies Review of subject diary: infusions, bleeding summary, efficacy assessment, adverse events, concomitant medications and compliance Investigator's assessment of efficacy Assessment of major and target joints
Pharmacokinetic Endpoints	The following PK endpoints will be calculated for subjects who complete the PK Phase: • Maximum post-infusion plasma concentration (C_{max}) • Incremental recovery • In vivo recovery (IVR) • 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 (MRT) • Elimination rate constant (λZ) • Terminal half-life ($t_{1/2}$) • Clearance (CL) • Volume of distribution at steady-state (V_{dss})
Efficacy Endpoints	**Primary Efficacy Endpoint:** • Annualized bleeding rate (ABR) **Secondary Efficacy Endpoints:** The following secondary efficacy endpoints are evaluated at the bleeding episode level: • Subject rating of efficacy • Change in pain • Change in swelling • Time from onset of bleeding to the first infusion • Time from onset of treatment until resolution of the bleeding episode • Number of infusions required to treat the bleeding episode The following secondary efficacy endpoints are evaluated at the subject level: • Investigator rating of APVO101 prophylaxis efficacy • Investigator rating of APVO101 efficacy for control and management of bleeding episodes **Exploratory Efficacy Endpoints:**

Title	**Evaluation of a Recombinant Factor IX Product, APVO101, in Previously-Treated Pediatric Patients with Hemophilia B**
	The following endpoints will be calculated for surgical procedures (if applicable): • Surgeon assessment of estimated blood loss at time of surgery • Surgeon assessment of post-surgery blood loss (at 12-hour and 24-hour post-surgery time points)
Safety Endpoints	The following assessments will be used to evaluate the safety: • Adverse events • Inhibitory factor IX antibodies • Non-inhibitory factor IX antibodies • Anti-CHOP antibodies • Thrombogenic markers
Statistical Methods	PK parameters will be listed and summarized. Descriptive statistics of PK parameters will be provided; no formal statistical test is planned. Descriptive summaries and listings will be provided for all efficacy endpoints. Summary statistics and listings will be provided for all safety endpoints. Also, incidence of non-inhibitory factor IX antibodies and incidence of anti-CHOP antibodies will be evaluated. Detailed description of the planned analyses will be provided in APVO101-903 statistical analysis plan (SAP).

Schedule of Events

Table 1: Schedule of Events for APVO101-903

	Screening[12]	PK Phase		Treatment Phase				Continuation Phase			End of Study or Early Termination
Evaluations		**Pre-infusion[1]**	**Post-infusion[2]**	**5 ED (±1 ED)**	**12 ED (±2 ED)**	**25 ED (±3 ED)**	**50 ED (±5 ED)**	**75 ED (±5 ED)**	**100 ED (±5 ED)**	**Every 3 months (~25 ED ±5 ED)**	
Informed consent and/or assent	X										
Eligibility Criteria Review	X										
Medical and hemophilia-related history	X	X									
Demographics (age, sex)	X										
Factor IX mutation assessment					X[10]						
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[3]			X	X	X	X	X	X
Thrombogenic markers[14]		X[14]	X[4,14]								
CBC with differential [5]	X					X[15]	X[15]	X[15]	X[15]	X[15]	X[15]
CD4 count[13]	X										
Serum chemistry[6]	X					X[15]	X[15]	X[15]	X[15]	X[15]	X[15]
Inhibitor titer and non-inhibitory factor IX binding antibodies[9]	X	X[9]		X	X	X	X	X	X	X	X
Anti-CHOP antibodies	X	X[16]		X	X	X	X	X	X	X	X
Assessment of major and/or target joints	X						X		X		X

Evaluations	Screening[12]	PK Phase		Treatment Phase				Continuation Phase			End of Study or Early Termination
		Pre-infusion[1]	Post-infusion[2]	5 ED (±1 ED)	12 ED (±2 ED)	25 ED (±3 ED)	50 ED (±5 ED)	75 ED (±5 ED)	100 ED (±5 ED)	Every 3 months (~25 ED ±5 ED)	
Urinalysis[7]	X					X	X	X	X	X	X
Factor IX activity[11]		X	X								
Adverse events	X		X	X	X	X	X	X	X	X	X
Efficacy/subject diary[8]	X			X	X	X	X	X	X	X	X
Training on subject diary and APVO101 reconstitution and administration	X										

[1] From 2 hours to 15 minutes pre-infusion.
[2] At 15-30 minutes, 4-6 hours, 24-26 hours and 46-50 hours post-infusion of 75 ± 5 IU/kg (PK dose).
[3] Vital signs (pulse rate, blood pressure, respiratory rate and temperature) at 15-30 minutes, 4-6 hours, 24-26 hours and 46-50 hours post-infusion of PK dose.
[4] Thrombogenicity marker assessments at 15-30 minutes, 4-6 hours and 24-26 hours post-infusion of PK dose.
[5] Includes hemoglobin, hematocrit, absolute counts of: white blood cells, neutrophils, monocytes, lymphocytes, eosinophils, basophils, platelets and red blood cells; mean platelet volume (MPV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) to be assessed at a local laboratory.
[6] Includes ALT, AST, ALP, BUN or urea, uric acid, creatinine, total bilirubin and glucose to be assessed at a local laboratory.
[7] Urine dipstick, followed by microscopy if abnormal to be assessed at a local laboratory.
[8] Investigator's efficacy assessment and review of subject's diary including infusions, bleeding summary, subject's efficacy assessment, adverse events and concomitant medications. At Screening, review of subject diary to include review of previous factor IX therapy (if available).
[9] Inhibitory and non-inhibitory factor IX antibodies to be assessed by central lab at PK Phase Pre-infusion for subjects weighing ≥ 28 kg, and all subjects at all other time points.
[10] Factor IX mutation assessment to include mutation genotyping by central laboratory if not previously documented. For patients below 10 kg this may be done at any time during the study when blood volumes allow
[11] Factor IX activity to be assessed by central lab pre-infusion and post-infusion at 15-30 minutes, 4-6 hours, 24-26 hours, and 46-50 hours. Pre-infusion and 15 to 30 minutes post-infusion samples will be tested for factor IX activity to determine the starting prophylaxis dose. See section 5.7.1 for further details.
[12] Screening to occur 21 to 5 days prior to PK phase.
[13] CD4 count to be assessed by local laboratory.
[14] See Table 2 for thrombogenicity assessments by subject weight; thrombogenicity markers include D-dimer, TAT complex, fragment 1+2.
[15] For patients below 17 kg, CBC with differential and serum chemistry should be collected if blood volumes allow.
[16] Anti-CHOP antibodies to be assessed by central laboratory at PK phase pre-infusion for subjects weighing ≥ 28 kg

Table 2: Thrombogenicity Assessments During PK Phase by Subject Weight

Subject weight	Pre-infusion	15-30 min post-infusion	4-6 hours post-infusion	24-26 hours post-infusion
≥ 20 kg	X	X	X	X
≥ 17 kg to <20kg	X	X		X
< 17 kg[1]				

[1] To accommodate blood volume limitations for subjects < 17 kg, no thrombogenicity assessments will be performed during the PK Phase. Thrombogenicity assessments may be drawn at these timepoints during the Treatment Phase when blood volume limitations allow.

Table 3: Schedule of Events for a Surgical Procedure (if required during Treatment Phase and/or Continuation Phase)

	Prior to surgery[1]		During surgery	End of surgery	12 hours post-surgery		24 hours post-surgery[2]		28 days (±7 days) post-factor IX replacement therapy for surgery
Evaluations	**Pre-infusion**	**Post-infusion (5-30 min)**			**Pre-infusion**	**Post-infusion (5-30 min)**	**Pre-infusion**	**Post-infusion (5-30 min)**	
Factor IX activity[3]	X	X	X[4]		X	X	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		

[1] If using bolus infusions, an infusion of up to 120 IU/kg will be given within 1 hour prior to the start of the procedure, followed by an infusion of approximately 60 IU/kg 12 hours after the first infusion and an infusion of up to 120 IU/kg 24 hours after the first infusion. If administering a continuous infusion, the plasma factor IX activity should range between 70% and 110%, and the dose and timing of subsequent infusions and adjustments should be recorded and guided by factor IX activity results.

[2] Continue with bolus or continuous infusion treatment for as long as the surgeon deems necessary, but for a minimum of 3 days post-surgery for major surgery or a minimum of 1 day post-procedure for minor surgery. Assess pre- and post-infusion factor IX activity every 12 hours.

[3] Factor IX activity is to be assessed by the local laboratory at all time points. If blood volumes allow, factor IX samples should also be assessed by the central laboratory.

[4] If study product is infused during surgery, measure factor IX activity pre- and post-infusion (5-30 minutes).

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ABR	Annualized bleed rate
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate aminotransferase
$AUC_{0\text{-day }7}$	Area under the plasma concentration curve from time 0 to day 7
$AUC_{0\text{-}\infty}$	Area under the plasma concentration curve from time 0 to infinity
$AUC_{0\text{-}t}$	Area under the plasma concentration curve from time 0 to the last measurable concentration
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of federal regulations title 21
Cl	Drug clearance rate
C_{max}	Maximum serum concentration
CHO	Chinese hamster ovary cells
CHOP	Chinese hamster ovary cell proteins
CRO	Contract research organization
CRF	Case report form
DIC	Disseminated intravascular coagulation
EC	Ethics committee
ED	Exposure day
EDC	Electronic data capture
EU	European Union
FIX	Factor IX
GCP	Good clinical practices
HIC	Hydrophobic interaction chromatography
EC	Ethics committee
ICF	Informed consent form
ICH	International conference on harmonization

IgG	Immunoglobulin G
IRB	Institutional review board
IV	Intravenous
PK	Pharmacokinetics
PIP	Pediatric Investigation Plan
PTP	Previously-treated patient
PTT	Partial thromboplastin time
SAE	Serious adverse event
SAP	Statistical analysis plan
TAT	Thrombin-antithrombin complex
V_{ss}	Volume of distribution at steady state
WHO	World Health Organization
WFH	World Federation of Hemophilia
WFI	Water for injection

1. BACKGROUND INFORMATION

1.1. Introduction

Hemophilia is an inherited clotting factor disorder; the two most prevalent types of hemophilia are types A and B (1). Hemophilia B (congenital factor IX deficiency) is usually caused by an X-linked recessive trait carried by females with one defective factor IX gene. Fifty percent of their male offspring will have the disease and 50% of their female offspring will be carriers. In about 30% of cases, there is no family history of the disorder and the condition results from spontaneous factor IX gene mutation. Hemophilia disorder occurs in about 1 out of 10,000 births; with hemophilia B being considered a rare disorder, representing 15–20% of hemophilia patients (2).

Severity of hemophilia B can be defined based on the level of factor IX (% of normal factor IX activity) as severe (< 1% factor IX activity), moderate (1–5% factor IX activity) or mild (5–40% factor IX activity) (3). Patients with < 2% but > 1% factor IX activity are sometimes referred to as moderately severe hemophilia B patients. Severe forms of hemophilia become apparent early in life, at circumcision, or when the infant becomes mobile, whereas mild cases may go unnoticed until they occur in response to surgery or trauma. In severe cases, internal bleeding may occur anywhere and bleeding into joints is common (3). Due to joint bleeding, problems associated with hemophilia include possible joint deformity, reductions in mobility and arthritis (4).

The primary aim of care for hemophilia patients is to prevent and treat bleeding with the deficient clotting factor, in case of hemophilia B, factor IX. People with hemophilia are best managed in a comprehensive care setting, however, whenever appropriate and possible, persons with hemophilia should be managed in a home therapy setting. Clinical study outcomes have demonstrated conclusively that immediate dosing of replacement factor concentrate at the initiation of a bleeding episode significantly minimizes the most significant morbidities associated with the condition (3).

The World Federation of Hemophilia (WFH) strongly recommends the use of viral-inactivated plasma-derived or recombinant concentrates for the treatment of hemophilia (3). The mainstay, with respect to treatment regimens, is prophylactic factor replacement to prevent anticipated bleeding. This prevents bleeding and joint destruction and should be the goal of therapy to preserve normal musculoskeletal function. The WFH recommends primary prophylaxis (start of prophylactic treatment after first joint bleed) or secondary prophylaxis (prophylactic regimen after second joint bleed) in pediatric patients < 12 years of age (3).

Prophylaxis is also recommended after the onset of joint disease (tertiary prophylaxis).

Ultimately, the dosing protocol for any patient should be individualized as much as possible based on age, weight, venous access, bleeding phenotype, activity, and availability of clotting factor concentrates (3).

Currently, there are five marketed recombinant factor IX products for use in children < 12 years of age with hemophilia B; two factor IX products produced in Chinese Hamster Ovary (CHO) cell lines with conventional half-life: BeneFIX® (nonacog alfa); marketed since 1997 in the United States (US) and European Union (EU), and RIXUBIS® (nonacog gamma); marketed since 2014 in the US and EU (5, 6) and three prolonged half-life factor IX products: ALPROLIX® (eftrenonacog alfa) a factor IX

molecule covalently linked to the Fc-domain of human IgG_1 and produced in a human embryonic kidney (HEK) cell line; and marketed since 2014 in the US, Canada, Japan and Australia, IDELVION® (albutrepenonacog alfa), generated by the genetic fusion of recombinant albumin to recombinant factor IX, produced in CHO cells, and marketed since 2016 in the US, EU, and Canada, and REBINYN® (nonacog beta pegol), a glycoPEGylated recombinant DNA-derived factor IX; marketed since 2018 in the US (7, 8, 9).

APVO101 (conventional half-life recombinant factor IX) is licensed in the US (as IXINITY®) for control and prevention of bleeding episodes, and for perioperative management in hemophilia B patients ≥ 12 years of age. Although APVO101 has been administered to pediatric previously-treated patients (PTPs) < 12 years of age during the clinical development (see Section 1.2.2), additional data in PTPs < 12 years of age are required to satisfy regulatory a post-marketing requirement (i.e., 20 pediatric [< 12 years of age] PTPs with 50 exposure days [ED]) (see Section 1.3).

1.2. Trial Drug

1.2.1. Description of Trial Drug

[redacted]

APVO101 has been developed as a lyophilized product, which, after reconstitution with sterile water-for-injection (WFI), is intended for intravenous (IV) administration. There are no novel excipients in the product formulation, and all excipients are generally regarded as safe (as per 21 CFR 330.1).

For more information, refer to Section 5.

1.2.2. Summary of Findings from Clinical Trials with APVO101

Pharmacokinetics (PK), safety and efficacy of APVO101 have been evaluated in study IB1001-01 with predominantly adolescent/adult (≥ 12 years of age) PTPs with severe or moderately severe (factor IX activity ≤ 2%) hemophilia B. A total of 77 subjects (in the US, Europe, Israel and India) were screened and enrolled in the study; there were three US subjects < 12 years of age who were enrolled into the study (exclusive of PK assessments). There were 32 subjects enrolled in a randomized PK Phase to evaluate non-inferiority of APVO101 to commercially available recombinant factor IX product (BeneFIX). The results of the PK Phase demonstrated that APVO101 is non-inferior to BeneFIX with respect to its pharmacokinetic profile, in particular $AUC_{0-\infty}$, $AUC_{0-72\ hours}$, and C_{max}. The incremental recovery (IU/dL per IU/kg) in adolescent and adult PTPs was 0.98. The initial PK

profile of APVO101 was comparable when repeated (n=14) 5.8 months (median) after its initial evaluation suggesting a stable profile over time and across product lots.

The majority of the PK subjects (n = 29) continued into the Treatment and Continuation phases of the study where long-term clinical efficacy and safety of APVO101 were evaluated; a total of 61 subjects received prophylaxis treatment (median dose: 53 IU/kg), while 12 subjects received on-demand (median dose: 57 IU/kg). There were 55 subjects with 50 ED to APVO101 and 45 subjects with 100 ED. The median annualized bleeding rate (ABR) for subjects on prophylaxis was 1.52, while for on-demand subjects it was 16.4. Overall, efficacy of APVO101 in the prevention and treatment of bleeding episodes has been shown to be satisfactory. This is supported by the investigator and subject assessments of APVO101 efficacy, by the demonstrated prevention of bleeding episodes in subjects on adequate and compliant prophylaxis regimens, and by control of hemorrhages.

In addition, APVO101 was well tolerated with no evidence of inhibitor development in any subject. Adverse drug reactions (i.e., adverse events related to APVO101) were reported in 3.3% of subjects, with headache being the most frequent adverse reaction (2.6% of subjects); all adverse drug reactions were mild or moderate.

As part of study IB1001-01, a surgery sub-study was conducted to evaluate APVO101 for perioperative management of major surgical procedures. APVO101 was administered during major surgical procedures as bolus (n = 13) or continuous infusion (n = 6). APVO101 was rated as adequate or better in controlling hemostasis post-surgery as assessed by the surgeon when used in various procedures, including, knee arthroplasty (n = 8), elbow arthroplasty (n = 2), knee amputation (n = 1), percutaneous Achilles tendon lengthening (n = 1), open inguinal hernia repair (n = 1), tibiotalar fusion (n = 1), arthroscopic synovectomy (n = 2), and debridement (ankle, knee) (n = 3). In all instances, blood loss at surgery was ‘expected’ or ‘less than expected’ as assessed by the surgeon. These data indicate that APVO101 can be effectively and safely used for perioperative management.

[redacted]

Furthermore, APVO101 has been evaluated for PK, safety and efficacy in study IB1001-02 with severe or moderately severe (factor IX activity ≤ 2%) hemophilia B PTPs < 12 years of age. Nine pediatric subjects (3 subjects < 6 years and 6 subjects 6-12 years) were enrolled in the study (all were prescribed a prophylaxis regimen following PK assessment; one subject erroneously received on-demand treatment).

The median ED for patients on prophylactic treatment was 221 (range 111-404) and the median time between first and last treatment was 46 months. The median total number of bleeds per patient was 1 (range 0-6); two patients experienced no bleeds. The median annualized bleed rate was 0.3 (range 0-1.6). The patient who received treatment on demand experienced 23 bleeds with an annualized bleed rate of 11. No adverse events related to APVO101 were reported. None of the patients developed factor IX inhibitors during the study.

[redacted]

For further summary of clinical trial data on APVO101, refer to the most current APVO101 Investigator's Brochure.

1.2.3. Benefit:Risk Ratio of APVO101

In its pivotal clinical trial (IB1001-01) in patients with hemophilia B aged ≥ 12-years-old, APVO101 was shown to have a non-inferior PK profile when compared to BeneFIX®. In addition, APVO210 was demonstrated to control and manage breakthrough and other bleeding episodes during the treatment phase (which included 3 patients < 12-years-old on an exception basis) and was assessed by surgeons to provide expected or better than expected hemostatic control during major surgical procedures. The most common adverse event related to APVO101 according to the investigator was headache which was reported by 2.6% of patients. Based on these data, APVO101 was FDA approved for marketing in the United States.

APVO101 has also been studied in 9 patients with hemophilia B < 12-years-old when used as prophylaxis (IB1001-02). In this preliminary study, APVO101 provided effective bleed prevention and management with a median number of ED of 221. There were no subjects who had drug-related adverse events.

There are potential risks with APVO101, as with any recombinant factor IX therapy. One potential risk is the development of factor IX inhibitory antibodies (inhibitors). To date, there have been no inhibitors reported in any APVO101 clinical trial or in post-marketing safety surveillance. Since the development of inhibitors is correlated with early treatment with factor IX, only subjects with at least 50 ED of a factor IX treatment will be allowed to participate. Subjects are also tested for inhibitors at screening and excluded if positive. Regular inhibitor testing is also done throughout the study.

Other factor IX class-specific risks include thromboembolic events, hypersensitivity (including anaphylaxis) and nephrotic syndrome. None of these adverse events have been seen in APVO101 clinical trials. There has been one post-marketing report of anaphylaxis in a patient who received

commercial APVO101 (IXINITY); however, this patient has also reported anaphylaxis with other factor IX therapies. This study includes testing of thrombogenic markers at the PK stage to evaluate for thrombotic risk. Serum chemistry and urinalysis are tested at Screening and regularly throughout the study to evaluate for renal (and other) effects. Subjects with known hypersensitivity to APVO101 or its excipients are excluded from this study, and subjects are followed frequently, especially during the start of the Treatment Phase, to monitor for any adverse events.

The safety and efficacy data from clinical studies of APVO101, along with its post-marketing safety data, support a positive benefit:risk profile for APVO101 for moderately-severe to severe hemophilia B patients < 12-years-old. Furthermore, this study is designed to exclude subjects at risk for class-related adverse events where possible and to monitor the safety of all subjects closely throughout the study.

1.3. Clinical Trial Rationale

The initiation of this study (APVO101-903) is based on safety and efficacy data from two clinical trials in previously treated adult, adolescent and pediatric patients with severe hemophilia B. In September 2014, the Data and Safety Monitoring Board reviewed the available polished APVO101 clinical trial safety, immunogenicity and efficacy data from two ongoing clinical trials (IB1001-01 and IB1001-02) and expressed no concerns, allowing the studies to continue and to recruit new subjects <12 years of age.

APVO101 is licensed in the US (as IXINITY®) for control and prevention of bleeding episodes, and for perioperative management in hemophilia B patients ≥12 years of age. However, as part of the post-marketing requirement for APVO101 in the US, the Food and Drug Administration (FDA) has requested data in 20 pediatric (< 12 years of age) patients followed-up for 50 ED. In addition, the European Medicines Agency (EMA) requires clinical investigation in PTP patients < 12 years of age for licensure of recombinant factor IX products for use in children. Currently, the requirements for the pediatric development are subject to an agreed Pediatric Investigation Plan (PIP) with the Pediatric Development Committee (PDCO) in the EU.

2. TRIAL OBJECTIVES AND PURPOSE

2.1. Primary Objectives

The following are the primary objectives of APVO101-903:

- To evaluate safety of APVO101 in pediatric subjects with hemophilia B for at least 50 ED
- To assess 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 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)

2.2. Exploratory Objectives

The following are exploratory objectives of APVO101-903:

- To evaluate markers of thrombogenicity [D-dimer, thrombin-antithrombin III complex (TAT) and fragment 1+2 (F1+2)] during the first 24 hours post-infusion of APVO101
- To evaluate efficacy of APVO101 for perioperative management in pediatric subjects with hemophilia B

3. TRIAL DESIGN

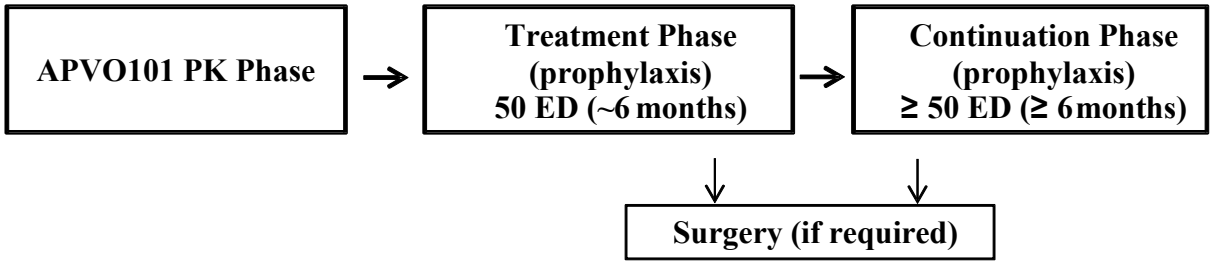
3.1. Trial Design

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

Study APVO101-903 consists of three distinct phases (Figure 1):

- PK Phase – PK evaluation will consist 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 – subjects will receive APVO101 prophylaxis (starting prophylaxis dose to be determined based on APVO101 recovery; ideally within the recommended dose range: 35 – 75 IU/kg; twice weekly) for 50 ED (approximately 6 months).
- Continuation Phase – subjects may continue to receive APVO101 prophylaxis (recommended dose range: 35 – 75 IU/kg; twice weekly) for an additional ≥ 50 ED.

Figure 1: Overview of APVO101-903 Design



The PK evaluation is 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 is expected to include a minimum of 6 months of APVO101 prophylaxis to obtain 50 ED, while the Continuation Phase is expected to include APVO101 prophylaxis for an additional ≥ 50 ED (≥ 6 months). Between 15 and 20 evaluable subjects are targeted to complete all phases of the study. Treatment with APVO101 to support a surgical procedure (if required) is permitted for subjects in Treatment/Continuation phases of the study.

The duration of subject study participation may vary depending on the time of enrollment into the study but is expected to be for at least 12 months.

3.2. Anticipated Centers

Study APVO101-903 is a multi-center trial with international investigational sites; exact locations and number of the sites are to be determined.

3.3. Sample Size

Up to 22 subjects will be enrolled in order to have 15 to 20 evaluable subjects (10 subjects < 6 years and 10 subjects 6 to < 12 years) complete the study (i.e., completion of PK assessments and a minimum of 50 ED), taking into consideration the very small size of the population available for clinical trials and the challenges of these trials in children, especially those under 6 years of age.

3.4. Criteria for Stopping or Terminating the Trial

Medexus and the principal investigator may elect to terminate the trial early as defined by the clinical trial agreement. The trial may be terminated at any or all sites for any of the following reasons:

- The safety data demonstrate or strongly suggest that the trial treatment (or participation in the trial) is unsafe. The investigator and sponsor will be responsible for ongoing review of safety data. The investigator will assess seriousness, causality and intensity (severity) of an adverse event.
- The protocol or conduct of the trial is flawed such that the safety or rights of the trial subjects may be adversely affected.
- The ethics committee has withdrawn the approval for the trial and has denied reconsideration.
- The investigational treatment is found to be ineffective.
- Poor recruitment.
- Relocation of the investigator or reallocation of investigator's responsibilities, or disqualification of the investigator.
- Non-adherence to the protocol or unavailability of the principal investigator or his staff for the sponsor's (or their authorized representative) monitoring personnel.
- Inadequate evidence of the Principal Investigator's personal conduct or supervision of the trial.
- Change of research strategy or change of management priorities.
- Imposition of clinical hold by a regulatory authority.

Any decision to voluntarily suspend or terminate a clinical trial will be carefully reviewed and fully justified. The sponsor will notify the FDA and other competent regulatory agencies and the Institutional Review Board (IRB)/Ethics Committee (EC) of any suspension or termination, along with justification for restarting or terminating the study as applicable.

The principal investigator must notify the IRB/EC in writing of the trial's completion or early termination. Medexus must receive a copy of the notification letter from the IRB/EC indicating receipt of the completion or early termination letter.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

The study population will consist of subjects who meet study eligibility requirements (inclusion and exclusion criteria) outlined in sections below. Eligibility criteria linked to laboratory test results will be discerned based on laboratory testing at Screening visit (Section 6.1). A subject will be considered 'enrolled' into the study after receiving first infusion of APVO101.

4.1. Subject Inclusion Criteria

The following conditions must be met before a subject may be enrolled in the study:

1. Age: < 11.5 years of age at the time of the first dose and < 12 years throughout the Treatment Phase of the study (for at least 50 ED).
2. Informed consent: subject's parent or legal guardian written Institutional Review Board (IRB)/Ethics Committee (EC)-approved informed consent. An assent form (IRB/EC-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 ED; approximately 6 months).
4. Documented severe or moderately severe hemophilia B diagnosis (factor IX 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 factor IX.
5. Subjects must be on prophylaxis or switch to a prophylaxis regimen for the duration of the study.
6. Previously treated patients with a minimum of 50 ED (as documented and determined by the investigator) to a preparation/blood components containing factor IX.
7. Willingness to adhere to the 4-day washout period of any factor IX replacement therapy prior to PK evaluation. In case of previous exposure to a factor IX product with a prolonged half-life, a washout period of 3 half-lives is required in order to achieve steady state factor IX level prior to exposure to APVO101.
8. Immunocompetent (CD4 count > 400/mm^3) and not receiving immune modulating or chemotherapeutic agents.
9. Platelet count at least 150,000/mm^3.
10. Liver function: alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 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.

4.2. Subject Exclusion Criteria

Any of the following conditions exclude a subject from the study:

1. History of factor IX inhibitor ≥ 0.6 Bethesda Units (BU); confirmed by the screening result.
2. Existence of another coagulation disorder.
3. Evidence of thrombotic disease, fibrinolysis, or disseminated intravascular coagulation (DIC).
4. Use of an investigational drug within 30 days prior to study entry.
5. Previous use of APVO101.
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 factor IX or recombinant factor IX that interfered with the subject's ability to treat bleeding episodes with a factor IX product.
11. History of any medical condition that would impact the efficacy evaluation and/or safety evaluation of the study product.

4.2.1. Subject Withdrawal

The subjects must be available, without coercion, for all parts of the trial.

If continued participation jeopardizes the subject's health, the subject should be withdrawn from the trial. The investigator is encouraged to consult the sponsor prior to the withdrawal of any subject, except in the event of a medical emergency. The reason for withdrawal of any subject must be clearly documented on the trial source documents and the appropriate data collection tools.

4.2.2. Subject Withdrawal Criteria

All subjects are free to withdraw from participation in this trial at any time, for any reason, specified or unspecified, and without penalty or loss of benefits to which the subject is otherwise entitled.

In addition, subjects may be withdrawn from the trial for any of, but not limited to, the following reasons:

- Protocol violation (non-compliance with medication or evaluation schedule with impact on subject risk-to-benefit or on protocol integrity)
- Serious illness that results in subject's inability to receive therapy or be evaluated per protocol requirements

- Discretion of Principal Investigator
- Voluntary withdrawal by subject or parent or legal guardian (efforts should be made to conduct a termination study visit)
- Death
- Sponsor terminates the study

Reason for withdrawal and the date of withdrawal should be documented. Medexus should be notified within 24 hours of all study withdrawals and every effort should be made to conduct an early termination evaluation.

The sponsor reserves the right to terminate the study or withdraw any subject from the study for any reason at any time.

If a subject is withdrawn from the trial, they will not be re-entered into the trial for any reason.

4.2.3. Subject Replacement

Subjects withdrawn from the trial or who withdraw consent prior to dosing will be replaced. Subjects withdrawn from the trial or who withdraw consent after dosing may be replaced.

Subjects are eligible to be rescreened for a screening failure only if the patient was unable to be enrolled during the screening period due to scheduling issues or due to bleeding. Subjects may be rescreened up to 3 times for these reasons.

4.2.4. Follow-up for Withdrawn Subjects

Every attempt will be made to ensure that subjects who are withdrawn, or who withdraw from the trial during the active treatment or follow-up period, will complete all safety and available efficacy assessments for the early withdrawal visit as outlined in this protocol. The investigator should inform the subjects and/or parent or legal guardian that these assessments are for their own safety.

5. TRIAL MEDICATION

APVO101 is a lyophilized coagulation factor IX (recombinant) for IV administration.

5.1. Packaging and Formulation

APVO101 is available in single-use vials containing the labeled amount of factor IX activity.

[redacted] There are no novel excipients in the formulation of APVO101 drug product and there are no particular concerns related to any of the ingredients for use in the pediatric population.

For more information, please refer to the current version of Investigator's Brochure for APVO101.

5.2. Labeling

APVO101 vial labels and shelf cartons will include information to comply with local regulations for the country in which the trial is conducted, in the appropriate language(s).

An example of information that may be included on vial label/shelf carton for APVO101:

- "Investigational Drug", "To Be Used by Qualified Investigator Only", "Caution: New Drug - Limited by Federal Law to Investigational Use" or similar wording
- The product strength/potency
- The lot number
- The date of manufacture and/or Expiry date
- The protocol code or identification
- The recommended storage conditions
- The name and address of the Manufacturer

5.3. Storage Conditions

APVO101 vials must be stored and transported at 2°C – 8°C. Do not freeze. Keep the APVO101 vials away from light.

Reconstituted APVO101 vials should not be refrigerated and must be used within 3 hours of reconstitution. The reconstituted APVO101 product must be at room temperature at time of infusion.

For further information, refer to the current version of Investigator's Brochure for APVO101.

5.4. Preparation and Administration

APVO101 is prepared by reconstituting lyophilized powder with sterile WFI. APVO101 reconstituted product must be at room temperature at time of infusion. Administration should occur at a maximum infusion rate of 10 mL/minute; product should be infused over a period of approximately five minutes.

Reconstitution and administration instructions for APVO101 are provided in the most current Investigator's Brochure for APVO101.

Site personnel will train the subject and/or parent or legal guardian on reconstitution and administration of APVO101 and assure that the subject and/or parent or legal guardian understands and is able to demonstrate the procedure. The instructions on how to reconstitute and administer the study drug will be provided to the subjects and parent or legal guardians.

5.5. Medication Shipment

APVO101 will be shipped to the site at a temperature of 2°C – 8°C. During shipment, the temperature of the drug will be monitored to ensure the required temperature conditions are maintained. The principal investigator or designate will be responsible for checking the number of vials and the condition of the vials received and entering this information into the drug accountability records, reporting the condition to Medexus and returning the data logger and all required documentation. Drug will be released for use by the site only after the data logger results are reviewed and written authorization has been issued to the Investigator/designate by the sponsor or designate. At the end of the trial, or upon request of the sponsor, all unused, partially used or empty vials will be returned to the sponsor or destroyed at the site as directed by Medexus.

5.6. Drug Accountability

The investigator is responsible for maintaining accurate inventory records of APVO101. The investigator or designate will inventory all APVO101 shipments upon receipt, acknowledge possession by signing all required documentation, and returning these to the sponsor. The investigator must ensure that all drug supplies are kept in a secure location in the site pharmacy in accordance with recommended storage conditions. A research pharmacist or a designated individual will maintain a current inventory and ongoing record of APVO101 using the Drug Accountability Form provided by the sponsor. This inventory record for the APVO101 will include:

- Protocol name, number and sponsor
- Product name and description
- Trial site and investigator name
- Product lot number and date of manufacture and/or Use-by/Expiry/Re-test date
- Number of vials dispensed, date and time of dispensing and study subject for whom product was dispensed
- Product balance
- Name and title of qualified individual dispensing product.

Subjects and/or their parent or legal guardian are instructed to return all used vials to the study site. An accounting of all returned and non-returned vials will be ongoing and will be noted on the Drug Accountability Form.

These records will be reviewed by representatives of the sponsor and may be reviewed by regulatory agencies.

5.7. APVO101 Dosing

5.7.1. Dose and Schedule

PK Phase

For the initial PK evaluation and after a 4-day washout period from previous factor IX replacement therapy or 3 half-lives washout of a factor IX product with a prolonged half-life, a member of the investigational site staff will administer a single IV 75 ± 5 IU/kg dose of APVO101.

Treatment Phase

After completion of PK Phase assessments, subjects will be treated with a prophylaxis regimen of APVO101. Subjects will receive a single IV dose of APVO101 twice weekly or at a frequency of infusions as determined appropriate by the investigator for the particular study subject for a total of 50 ED. The starting prophylaxis dose will be based on APVO101 recovery from PK Phase assessments (only pre-infusion and 15-30 minute post-infusion samples); ideally within the recommended dose range: 35 – 75 IU/kg, twice weekly). Samples for APVO101 recovery (only pre-infusion and 15-30 minutes post-infusion from the PK assessment) will be processed by the local laboratory and tested by the central laboratory. In the event the central laboratory is unable to provide the PK data in time to calculate the starting prophylaxis dose, the dosage and administration instructions found in the package insert for the U.S. approved product (IXINITY®) should be followed. Once PK data are available, the prophylaxis dose may be adjusted if needed.

Refer to the Dosage and Administration section in the package insert and Pharmacy Manual for more information.

For treatment and control of breakthrough, spontaneous or trauma-related bleeding episodes, the dose should be based on severity of bleeding episodes; see below:

- Minor bleeding episodes [e.g., uncomplicated hemarthroses and superficial muscle (except iliopsoas) with no neurovascular compromise, other soft tissue bleeds] and/or moderate bleeding episodes (e.g., hemarthrosis of longer duration, recurrent hemarthrosis, mucous membranes, deep lacerations, hematuria): 40 – 60 IU/kg
- Major or life-threatening bleeding episodes (e.g., iliopsoas, deep muscle with neurovascular injury, substantial blood loss, central nervous system, pharyngeal, retropharyngeal, retroperitoneal): 60 – 100 IU/kg

During APVO101 prophylaxis treatment and/or APVO101 treatment for control and management of bleeding episodes, every effort will be made to ensure that the prescribed dose per kilogram body weight is given. However, since it may be difficult to determine fractions of a vial for purposes of

providing an exact dose, it is acceptable to round up or down to the nearest vial. The process of rounding up or down should not, however, result in the study subject receiving > 120% or < 90% of the prescribed dose. The exact amount of factor IX infused must be recorded.

Continuation Phase

Following completion of the Treatment Phase (i.e., 50 ED), the investigator will assess the subject's dose and either assign the most recent dose from Treatment Phase or modify the dose if clinically indicated (see Section 5.7.2). The Continuation Phase dose should be within the recommended dose range of 35 – 75 IU/kg, twice weekly.

For treatment and control of breakthrough, spontaneous or trauma-related bleeding episodes, the dose should be based on severity of bleeding episodes; see below:

- Minor and/or moderate bleeding episodes: 40 – 60 IU/kg
- Major or life-threatening bleeding episodes: 60 – 100 IU/kg

Surgery

In the event of a minor or major surgery during the course of study participation (Treatment/ Continuation phases), use of either bolus or continuous infusion of APVO101 for surgical coverage is permissible.

Examples of major surgical procedures include synovectomy, knee or hip replacement, total tooth extraction, tonsillectomy and/or adenoidectomy, surgery for intracranial hemorrhage, radial head excision, arthrodesis, ankle surgery, abdominal surgery, herniorrhaphy, or surgery for major muscle bleed management. The following dosing is recommended for major surgical procedures:

- If using bolus infusions, an infusion of up to 120 IU/kg will be given within 1 hour prior to the start of the procedure, followed by an infusion of approximately 60 IU/kg 12 hours after the first infusion, and up to 120 IU/kg 24 hours after the first infusion, depending on the subject's post-infusion factor IX activity. This regimen of bolus infusions will continue every 12 hours as long as the physician and surgeon deem necessary, but for a minimum of 3 days post-procedure for major surgery or a minimum of 1 day post-procedure for minor surgery.
- If administering a continuous infusion, it will also continue for a minimum of 3 days post-procedure for major surgery or a minimum of 1 day post-procedure for minor surgery. The infusion rate, dose and timing of subsequent infusions and adjustments in dosing will be recorded and guided by factor IX assay results, with the doses of APVO101 administered appropriately to ensure that the plasma factor IX level does not drop below 60%. If continuous infusion is used, the plasma level of factor IX should range between 70% and 110%.

5.7.2. Dose Modifications

If clinically indicated, more or less frequent infusions or a variation of the recommended dose may be prescribed at the discretion of the investigator. The decision to do so will be based upon a host of

determinants, including pre- and/or post-dose Factor IX 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, 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- APVO101 infusion factor IX activity (i.e., APVO101 recovery) are recommended (when feasible) to determine dose modifications. The precise reason for doing so must be recorded in the case report form (CRF).

5.7.3. Treatment Compliance

PK Phase, Surgery (if required):

Because APVO101 treatment will be administered intravenously in a clinical setting for PK assessments and during surgical procedure(s), compliance with treatment is not expected to be an issue. However, it will be important during the washout period for the subject and within the 50-hour period post-PK APVO101 infusion to refrain from using factor IX products unless it is necessary to treat a bleeding episode. In such a case, the washout period will be re-started after the last infusion for treating the bleeding episode has been administered. Use of a non-study factor IX product is not permitted; however, if such an instance occurs, the details, including product name, dose, and reason for use, are to be documented.

Treatment Phase and Continuation Phase

Throughout the study, subjects/subjects' parents or legal guardians will maintain a diary of bleeding episodes, including usage (compliance) and tolerance of APVO101. In addition, subjects/subjects' parents or legal guardians will be asked to account for all used vials (i.e., return all vials to the site). The subjects/subjects' parents or legal guardians will be asked to record AEs and concomitant medications between visits. An evaluation of efficacy will also be recorded. Use of a non-study factor IX product is not permitted; however, if such an instance occurs, the details, including product name, dose, and reason for use, are to be documented.

The investigator or study coordinator will review the diary with the study subject/subject's parents or legal guardians at each visit. This collaborative review is intended to identify treatment-related problems, to evaluate compliance, and to reinforce adherence to the prophylaxis regimen. Additionally, during this diary review, site staff will reinforce the importance of complete documentation.

The study protocol specifies that each study subject will receive APVO101 on a prophylaxis schedule. In the event that this schedule is not followed, documentation of the reasons and circumstances altering the schedule will be recorded. In the event that the subject, his parent or legal guardian, or treating physician changes the prophylaxis regimen including one of 'on demand therapy', details of each bleed and response to APVO101 treatment will be recorded. In addition, the reasons for changing the prophylaxis schedule or changing to 'on demand therapy' will be recorded.

6. TRIAL PROCEDURES

6.1. Screening (21 to 5 days prior to PK Phase)

Eligible subjects and their parent or legal guardian will first undergo informed consent counselling. Once informed consent and assent (as applicable) have been obtained from subjects and parent or legal guardian, subjects will undergo a screening visit to ascertain their eligibility in this trial. The screening visit assessments will include:

1. Signed and dated Informed Consent Form (ICF) and assent form (as applicable)
2. Inclusion/exclusion criteria review.
3. Medical and hemophilia-related history, including documentation of factor IX genotype mutation, bleeding episode(s), documentation of PK data (e.g., recovery and half-life) utilizing prior non-study factor IX therapy, and documentation of at least 50 ED of factor IX replacement therapy
4. Concomitant medications
5. Demographics (age, sex)
6. Physical exam, vital signs, body weight and height
7. Local laboratory assessments:
    a. Serum chemistry [ALT, AST, alkaline phosphatase (ALP), blood urea nitrogen (BUN) or urea, uric acid, creatinine, total bilirubin, and glucose]
    b. Complete blood count (CBC) with differential [hemoglobin, hematocrit, absolute counts and/or percent of: white blood cells, neutrophils, monocytes, lymphocytes, eosinophils, basophils, platelets and red blood cells; mean platelet volume (MPV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC)]
    c. CD4 count
    d. Urinalysis [urine dipstick, followed by microscopy if abnormal]
8. Central laboratory assessments:
    a. Inhibitory factor IX antibodies (Nijmegen modified Bethesda assay)
    b. Non-inhibitory factor IX binding antibodies
    c. Anti-CHOP antibodies
9. Review of subject diary of previous factor IX therapy (if available): infusions, bleeding summary, subject's efficacy assessment, adverse events, and concomitant medications.
10. Investigator's assessment of efficacy of previous factor IX therapy
11. Assessment of major and target joint(s)

12. Assessment of adverse events
13. Review of study requirements, subject diary instructions, and training on APVO101 reconstitution and administration

6.2. Pharmacokinetic (PK) Phase Assessments

After a 4-day washout of factor IX replacement therapy or 3-half-lives washout of a factor IX product with a prolonged half-life, the following assessments will be evaluated. Given pediatric blood volume limitations, the number and timing of thrombogenicity marker assessments varies by subject weight (see Table 2).

Pre-infusion (2 hours to 15 minutes prior to infusion)

1. Physical exam, vital signs, body weight, height, concomitant medications, updated medical history (if applicable)
2. Central laboratory assessments:
    a. Inhibitory factor IX antibodies (Nijmegen modified Bethesda assay: for subjects weighing > 28 kg)
    b. Non-inhibitory factor IX binding antibodies (for subjects weighing > 28 kg)
    c. Anti-CHOP antibodies (for subjects weighing > 28 kg)
    d. Factor IX activity
    e. Thrombogenicity markers (See Table 2)

Post-infusion (75 ± 5 IU/kg)

1. Central laboratory assessments:
    a. Factor IX activity at the following time points post-infusion: 15-30 minutes, 4-6 hours, 24-26 hours and 46-50 hours
    b. Thrombogenicity markers [D-dimer, thrombin:antithrombin (TAT) complex and fragment 1+2] at 15-30 minutes, 4-6 hours and 24-26 hours post-infusion (See Table 2)
2. Vital signs at each PK time-point post-infusion
3. Assessment of adverse events

Note: pre-infusion and 15-30 minute post-infusion samples will be tested for factor IX activity to determine starting prophylaxis dose. See section 5.7.1 for further details.

6.3. Treatment Phase Assessments

After the start of APVO101 prophylaxis treatment regimen, the following assessments will be performed at:

5 ED (± 1 ED) and 12 ED (± 2 ED)

1. Central laboratory assessments:
    a. Inhibitory factor IX antibodies (Nijmegen modified Bethesda assay)
    b. Non-inhibitory factor IX binding antibodies
    c. Anti-CHOP antibodies
    d. Mutation genotyping (12 ED visit only, if not documented); for patients below 10 kg this may be done at any time during the study when blood volumes allow
2. Review of subject diary: infusions, bleeding summary, subject's efficacy assessment, adverse events, concomitant medications and compliance
3. Concomitant medications
4. Assessment of adverse events
5. Investigator's assessment of efficacy

25 ED (± 3 ED) and 50 ED (± 5 ED)

1. Physical exam, vital signs, body weight, and height
2. Concomitant medications
3. Local laboratory assessments:
    a. Serum chemistry (for patients below 17 kg, collect if blood volumes allow)
    b. Complete blood count (CBC) with differential (for patients below 17 kg, collect if blood volumes allow)
    c. Urinalysis [urine dipstick, followed by microscopy if abnormal]
4. Central laboratory assessments:
    a. Inhibitory factor IX antibodies (Nijmegen modified Bethesda assay)
    b. Non-inhibitory factor IX binding antibodies
    c. Anti-CHOP antibodies
5. Review of subject diary: infusions, bleeding summary, subject's efficacy assessment, adverse events, concomitant medications and compliance
6. Assessment of adverse events
7. Investigator's assessment of efficacy
8. Assessment of major and target joints (50 ED only)

6.3.1. Surgery Assessments

Treatment with APVO101 to support a minor or major surgical procedure (if required) is permitted for subjects in Treatment Phase. The following assessments will be performed for surgical procedure(s):

Prior to surgery; pre-infusion (2 hours to 15 minutes before infusion)

1. Documentation of planned surgery including rationale (may occur at any time prior to surgery)
2. Surgeon's assessment of expected/estimated blood loss for the surgical procedure (may occur at any time prior to surgery)
3. Local laboratory assessment:
    a. Factor IX activity
4. Central laboratory assessments:
    a. Factor IX activity (if blood volumes allow)
5. Vital signs

Prior to surgery; 5 – 30 minutes post-infusion (bolus)

1. Local laboratory assessment:
    a. Factor IX activity
2. Central laboratory assessment:
    a. Factor IX activity (if blood volumes allow)
3. Assessment of adverse events

During surgery

1. If study product is infused during surgery, local laboratory assessment
    a. Factor IX activity pre- and post-dose (5-30 minutes)
2. Assessment of adverse events
3. Use of blood products

End of surgery

1. Surgeon's assessment of total blood loss for the surgical procedure
2. Assessment of adverse events
3. Use of blood products

Post-surgery

12 hours (±2 hours) post-initial infusion; pre-infusion

1. Local laboratory assessment:
    a. Factor IX activity
2. Central laboratory assessment:
    a. Factor IX activity (if blood volumes allow)
3. Vital signs

4. Surgeon's assessment of blood loss
5. Use of blood products

12 hours post-initial infusion (±2 hours); 5 – 30 minutes post-infusion (bolus)

1. Local laboratory assessment:
    a. Factor IX activity
2. Central laboratory assessment:
    a. Factor IX activity (if blood volumes allow)
3. Assessment of adverse events

24 hours post-initial infusion (±3 hours); pre-infusion

1. Local laboratory assessment:
    a. Factor IX activity
2. Central laboratory assessment:
    b. Factor IX activity (if blood volumes allow)
3. Vital signs
4. Surgeon's assessment of blood loss
5. Use of blood products

24 hours post-initial infusion (±3 hours); 5 – 30 minutes post-infusion (bolus)

1. Local laboratory assessment:
    a. Factor IX activity
2. Central laboratory assessment:
    a. Factor IX activity (if blood volumes allow)
3. Assessment of adverse events

Factor IX activity (local laboratory assessment) should be monitored every 12 hours (±2 hours) thereafter (for a minimum of 3 days post-surgery or until healing in case of a major surgery or a minimum of 1 day post-procedure for minor surgery). Factor IX activity should be assessed before and within 30 minutes post-infusion of study product. If blood volumes allow, Factor IX activity should also be assessed by central laboratory at each timepoint. Adjustments in APVO101 dosing and timing post-surgery of each adjustment should be documented. Adverse events should be assessed for the duration of each continuous infusion period (±2 hours).

For continuous infusions, factor IX activity (local laboratory assessment), assessment of vital signs and use of blood products (pre-infusion) should be performed at 12-hour (±2 hours) and 24-hour (±3 hours) time points post-surgery and subsequently on a daily basis or more frequently if needed until continuous infusion is discontinued. If blood volumes allow, Factor IX activity should also be

assessed by central laboratory at each timepoint. Adjustments in APVO101 dosing and timing post-surgery of each adjustment should be documented. Adverse events should be assessed for the duration of each continuous infusion period (±2 hours).

In case of a major surgery (supported by bolus or continuous infusions), surgeon's assessment of blood loss should be performed every 12 hours (±2 hours) for at least 3 days post-surgery or until healing (if applicable).

28 days (±7 days) post-factor IX replacement therapy for surgery

1. Use of blood products

6.4. Continuation Phase Assessments

Treatment with APVO101 beyond 50 ED (accumulated during the Treatment Phase) will constitute Continuation Phase treatment.

Following 50 ED visit, subjects will be assessed at 75 ED (± 5 ED), 100 ED (± 5 ED) and every 3 months (~25 ED ± 5 ED) thereafter until end of study (*note: subjects may continue on study until last-subject-in completes 100 ED visit*) for the following:

1. Physical exam, vital signs, body weight and height
2. Concomitant medications
3. Local laboratory assessments:
    a. Serum chemistry (for patients below 17 kg, collect if blood volumes allow)
    b. Complete blood count (CBC) with differential (for patients below 17 kg, collect if blood volumes allow)
    c. Urinalysis [urine dipstick, followed by microscopy if abnormal]
4. Central laboratory assessments:
    a. Inhibitory factor IX antibodies (Nijmegen modified Bethesda assay)
    b. Non-inhibitory factor IX binding antibodies
    c. Anti-CHOP antibodies
5. Review of subject diary: infusions, bleeding summary, subject's efficacy assessment, adverse events, concomitant medications and compliance
6. Assessment of adverse events
7. Investigator's assessment of efficacy
8. Assessment of major and target joints (100 ED only)

6.4.1. Surgery Assessments

Treatment with APVO101 to support a minor or major surgical procedure (if required) is permitted for subjects in Continuation Phase. Refer to Section 6.3.1 for assessments to be performed for surgical procedure(s).

6.5. End of Study or Early Withdrawal Assessments

At the end of the study, or for subjects who prematurely terminate or who are withdrawn before the study is complete, the following will be evaluated:

1. Physical exam, vital signs, body weight and height
2. Concomitant medications
3. Assessment of adverse events
4. Local laboratory assessments:
    a. Serum chemistry (for patients below 17 kg, collect if blood volumes allow)
    b. CBC with differential (for patients below 17 kg, collect if blood volumes allow)
    c. Urinalysis [urine dipstick, followed by microscopy if abnormal]
5. Central laboratory assessments:
    a. Inhibitory factor IX antibodies (Nijmegen modified Bethesda assay)
    b. Non-inhibitory factor IX binding antibodies
    c. Anti-CHOP antibodies
6. Review of subject diary: infusions, bleeding summary, efficacy assessment, adverse events, concomitant medications and compliance
7. Investigator's assessment of efficacy
8. Assessment of major and target joints

6.6. Handling of Samples

Refer to the APVO101-903 Laboratory Manual on how to handle samples for central laboratory analyses during each phase of the study. Local laboratory samples should be handled by site standard procedures.

6.7. Shipment of Samples

Refer to the APVO101-903 Laboratory Manual on how to ship samples for central laboratory analyses during each phase of the study. Local laboratory samples should be transported according to site standard procedures.

6.8. Concomitant Medications

Any medication taken by the subject, including herbal preparations and non-prescription medications, within 15 days prior to screening and during the course of the trial and the reason for concomitant medication use, will be recorded on the trial source documents and concomitant medications page of the CRF.

6.9. Excluded Concomitant Medications

The following treatments are not permitted during the study:

- Agents impacting the hemostatic system (e.g., aspirin)
- Immunosuppressive drugs (e.g., steroids such as prednisone, chemotherapeutic agents)
- All other factor IX therapies (e.g., plasma-derived or recombinant factor IX products)

7. ASSESSMENT OF APVO101 PHARMACOKINETICS

Factor IX concentration levels are the basis for all PK parameter calculations.

Incremental recovery will be determined, as will the maximum plasma concentration (C_{max}) and the half-life ($t_{1/2}$). The area under the concentration time curve from time 0 to infinity ($AUC_{0-\infty}$) will be determined by the trapezoidal rule and the clearance (Cl) and volume of distribution at steady-state (Vd_{ss}) will be calculated from this number. Refer to Section 11.2.1 for PK endpoints.

8. ASSESSMENT OF APVO101 EFFICACY

8.1. Subject's Assessment of Efficacy

Throughout the study, subjects and/or their parent or legal guardian will maintain a subject diary to record information about each APVO101 infusion, any AEs and all bleeding episodes (trauma or spontaneous). An assessment of efficacy will be made for each bleeding episode. In the event of trauma, details will be recorded.

Within 6 hours (exact time to be recorded) after the subject believes the bleeding has stopped, an overall evaluation of efficacy of treatment will be provided. This will be done using the following verbal descriptors:

- 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

In addition to the description of efficacy, the subject and/or their parent or legal guardian will indicate the following:

- How long it took the bleeding to stop
- How long it took the pain to stop
- How long it took the swelling (if present) to resolve

This will be done for each variable using a series of check boxes for time intervals ranging from < 2 hours to 72+ hours after the onset of the bleeding episode.

The study investigator will be contacted by the subject, if efficacy of two consecutive APVO101 infusions is rated as 'fair' or 'poor'. The subject will be instructed to call the treatment center if there is an occurrence of 'poor' or no response to the therapy (i.e., sub-optimal response; see Section 8.2) for a specific bleeding episode.

The subjects and/or their parent or legal guardian will document in the diary if no bleeding episodes occurred.

8.2. Investigator's Assessment of Efficacy

At each study visit [during Treatment Phase and Continuation Phase; see Table 1], the investigator will make an assessment of APVO101 prophylaxis efficacy and an assessment of efficacy for control of bleeding episodes [if bleeding episode(s) are reported by the subject and/or their parent or legal guardian during the period]. The assessment will be based on the recording of events in the diary (i.e., review of subject diary) and discussion with the study subject and/or their parent or legal guardian.

The investigator will indicate the overall assessment of APVO101 prophylaxis efficacy, considering the absence of bleeding episodes, site, severity and types of bleeding episodes treated, and other factors that might influence the therapeutic response. In addition, when bleeding episode(s) are reported by the subject and/or their parent or legal guardian, the investigator will also rate the APVO101 efficacy for control and management of bleeding episode(s) treated. The investigator will consider the site, severity and type of the bleeding episodes reported by the subject and/or their parent or legal guardian when evaluating efficacy of APVO101 for control and management of bleeding episodes.

The investigator's efficacy assessment categories for prophylaxis and control of bleeding episodes will include: 'effective', 'partially effective' and 'not effective'.

If, in the estimation of the investigator, the response has been sub-optimal (i.e., an occurrence of 'poor' or 'no response' to the therapy for a specific bleeding episode as reported by the subject and/or their parent or legal guardian), this will be recorded and the reason for this assessment will be specified. In such an event (sub-optimal response), the investigator will review the circumstances surrounding the bleed and its response to therapy. Information collected shall include the following:

- Site of the bleed
- Cause and extent of injury
- Past history of bleeds at the anatomical site (determined by the investigator from subject's medical and hemophilia-related history and from the review of subject's diary while on study)
- Relevant clinical issues at the site for that bleed (e.g., in the case of a joint bleed, if the joint is a target joint, the extent of pain, joint swelling, and dysfunction over time (determined by the investigator from subject's medical and hemophilia- related history)
- Specifics of the management administered to that point

If a sub-optimal response to treatment is observed in two separate bleeding episodes in the same subject over the course of the study, this will be reported as an AE, although the investigator will have the option of reporting a sub-optimal response to one bleed as an AE.

In the case of a sub-optimal response, the investigator is encouraged to perform a test for inhibitory factor IX antibodies and APVO101 recovery (75 ± 5 IU/kg; factor IX measurements pre-infusion and at 15-30 minutes post-infusion). Samples for APVO101 recovery determination will be processed locally and tested locally and by the central laboratory.

The test for inhibitory factor IX antibodies will be completed locally and by the central laboratory. A repeat test will be performed by the central laboratory in case of a positive inhibitor test result by the central laboratory within 2 weeks of the study site notification of the original positive local laboratory result. Subjects who develop an inhibitor that changes from a low (≤ 5 BU) to a high titer (> 5BU) inhibitor or from a high titer to a low titer upon a second evaluation should return to the study site within two weeks of the second inhibitor assessment, for a third inhibitor test with a suggested minimum wash-out period of 72 hours. Once a low (0.6 to 5 BU) or a high titer (> 5 BU) inhibitor is confirmed, the subject will be withdrawn from the study. Any inhibitor confirmed by the central laboratory must be reported as a serious adverse event (SAE).

8.3. Surgeon's Assessment of Efficacy

APVO101 will be evaluated for success in providing coverage for surgical procedures (if required during Treatment/Continuation phases of the study). This will be assessed by the surgeon as follows:

- Estimation of expected blood loss prior to surgery (prior to infusion of APVO101), and actual blood loss during surgery, at the end of surgery, 12 hours and 24 hours post- surgery or every 12 hours for at least 3 days post-surgery or until healing in case of a major surgery, as 'less than expected', 'expected', or 'more than expected'
- Estimation of blood loss post-surgery at 12 hours and 24 hours post-surgery or every 12 hours for at least 3 days post-procedure or until healing in case of a major surgery, as 'hemostasis superior', 'hemostasis adequate', or 'hemostasis poorly controlled'

The surgeon will estimate the expected blood loss at the time of surgery (prior to infusion of APVO101) by taking into consideration the planned surgical procedure in a hemostatically normal male individual of the same demographics as the study subject for the intra-operative period, and, if applicable, for the post-operative period until drain removal and/or healing.

During the surgery, the surgeon should evaluate blood loss as per standard of care for the surgical procedure and the discretion of the surgeon.

At the end of the surgery, the surgeon will assess total blood loss for the surgical procedure and record the use of blood products for the duration of the surgical procedure (if applicable).

The use of and volume of blood products during the perioperative period (first 24 hours) and during the healing phase (see Table 3) will be recorded as an indicator of APVO101 hemostatic efficacy.

9. ASSESSMENT OF SAFETY

Safety throughout the clinical trial will be evaluated by assessment of the following:

- Adverse events (AEs)
  - All AEs will be reported by investigators and subjects and/or their parent or legal guardian. AEs are to be elicited by the investigator (or designate) asking the subject and/or their parent or legal guardian non-leading questions. Subjects and/or their parent or legal guardian will record AEs in the subject diary and the information will be reviewed by the investigator during each scheduled visit.
- Physical exams
- Vital signs (pulse rate, blood pressure, respiratory rate and temperature)
- Laboratory assessments, including:
  - Thrombogenic markers (D-dimer, TAT complex and fragment 1+2)
  - Serum chemistry (ALT, AST, ALP, BUN or urea, uric acid, creatinine, total bilirubin and glucose)
  - CBC with differential [hemoglobin, hematocrit, absolute counts of: white blood cells, neutrophils, monocytes, lymphocytes, eosinophils, basophils, platelets and red blood cells; mean platelet volume (MPV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC)]
  - Urinalysis [urine dipstick, followed by microscopy if abnormal]
  - Immunogenicity (inhibitor titer, non-inhibitory factor IX binding antibodies, and anti-CHOP antibodies)

Any clinically significant changes (as determined by the investigator) in laboratory test results, vital signs or physical exam must be captured as adverse events.

The above listed safety assessments will be evaluated at pre-determined time points during the conduct of the trial (see Table 1 and Table 3).

The central laboratory will create a distribution of values for all three thrombogenic markers (D-dimer, TAT complex, and fragment 1+2) based on negative controls (human plasma). The cut-off point for positivity will be defined as any value beyond the 99th percentile of the distribution of values for the negative controls for that particular parameter.

9.1. Definitions of Adverse Event, Serious Adverse Event and Adverse Drug Reaction

The occurrence of AEs, serious AEs (SAEs) and adverse drug reactions (ADRs) will be monitored throughout all phases of the trial and will cover all participating subjects. The definitions for AE, SAE and ADR are provided in Section 9.1.1, Section 9.1.2 and Section 9.1.3, respectively.

The relationship and relatedness of the AE to APVO101 is to be judged by the investigator as defined in Section 9.2.2.

9.1.1. Definition of an Adverse Event

An adverse event (AE) is defined as any untoward, undesirable, or unintended medical occurrence in a clinical trial subject administered APVO101 which does not necessarily have a causal relationship with APVO101. For purposes of this clinical trial, an AE can therefore be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of APVO101, whether or not related to the product.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency or intensity of the condition
- Significant or unexpected worsening or exacerbation of the condition/indication under study (hemophilia B)
- A new condition detected or diagnosed after study product administration even though it may have been present prior to the start of the study
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study product or a concurrent medication ("overdose" per se, should not be reported as an AE)
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (e.g., invasive protocol-defined procedures, modification of a subject's previous drug treatment regimen)
- A sub-optimal response to APVO101 treatment observed in two separate bleeding episodes in the same subject over the course of the study; although, the investigator will have the option of reporting a sub-optimal response to one bleed as an AE.
- A thromboembolic event (TEE)
- Nephrotic syndrome
- Hypersensitivity reaction, allergic reaction, anaphylaxis, anaphylactic shock; including, but not limited to symptoms of difficulty breathing, shortness of breath, swelling, hives, generalized urticaria, tightness of the chest, bronchospasm, laryngospasm, wheezing, hypotension, blurred vision
- Severe anaphylaxis; symptoms may include severe hives, severe swelling, severe chest tightness, difficulty breathing, wheezing, faintness, rapid heart rate, and low blood pressure

An AE **does not** include:

- Medical or surgical procedures (e.g., colonoscopy or biopsy); the medical condition that leads to the procedure is an AE
- Social or convenience hospital admissions where an untoward medical occurrence did not occur
- Day-to-day fluctuations of a pre-existing disease or conditions present or detected at the start of the study that do not worsen
- The disease/disorder being studied (hemophilia B), or expected progression, signs, or symptoms of the disease/disorder being studied (e.g., bleeding episodes) unless more severe than expected for the subject's condition

All AEs that occur after informed consent/assent is signed will be recorded in the source documents and on the appropriate CRF page.

In addition, all hypersensitivity and allergic reactions, anaphylaxis, and/or anaphylactic shock reactions will be recorded on the APVO101 Hypersensitivity Reaction Reporting Form; this form will be transmitted to Medexus Pharmacovigilance within 24 hours of the occurrence using the contact information below:

[redacted]

The information to be collected includes the nature, date and time of onset, intensity, duration, causality, and outcome of the event. Even if the AE is assessed by the investigator as not reasonably attributable to APVO101, its occurrence must be recorded in the source documents and on the appropriate page of the CRF.

Treatment-emergent AEs will be defined as AEs that occur after the first infusion with APVO101.

9.1.2. Definition of a Serious Adverse Event

A serious AE (SAE) is defined as a noxious and unintended response occurring at any dose that results in any of the following outcomes: death, life threatening experience, in-patient hospitalization or prolongation of existing hospitalization, a persistent or a significant disability/incapacity, or a congenital anomaly/birth defect.

Important medical events which may not result in death, be life threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

For the purposes of this clinical trial, development of an inhibitor (as determined by the central laboratory) while on study drug treatment will be considered an SAE.

NOTE: Death is an outcome and not an event. The condition leading to death is the event. Death will be considered an event only when no other information regarding the cause of death is available.

Hospitalization that is planned before inclusion into the study or outpatient treatment without overnight hospitalization is not considered a SAE. Hospitalization that occurs during a trial for social reasons (e.g., transportation difficulties, respite care) is not considered to be a SAE.

9.1.3. Definition of an Adverse Drug Reaction

An adverse drug reaction (ADR) is defined as an unwanted response to APVO101 which is noxious and unintended response to APVO101 and which occurs at doses normally used in humans for prophylaxis, diagnosis, for therapy of disease or modification of physiological function.

Expected ADRs are defined as ADRs whose nature (i.e., specificity or outcome), severity or frequency is consistent with the term or description used on the most current APVO101 Investigator's Brochure.

Unexpected ADRs are defined as ADRs whose nature (i.e., specificity or outcome), severity or frequency is either not identified, or is not consistent with the term or description used in the most current APVO101 Investigator's Brochure.

9.2. Assessment of Severity (Intensity) and Causality

All AEs, including those that are not of a serious nature and those that are expected, will be documented by the investigators (or designates) in the source documents and appropriately transcribed onto separate data forms provided for this purpose.

All AEs will be examined by the investigator or designate for assessment of both severity and causality using the criteria outlined in Section 9.2.1 and Section 9.2.2, respectively.

9.2.1. Assessment of Severity (Intensity)

Severity relates to the intensity of an AE. Adjectives used to describe the severity of an AE include mild, moderate, or severe. These are defined below.

Mild: awareness of a sign or symptom but subject can tolerate.

Moderate: discomfort enough to cause interference with normal daily activity.

Severe: resulting in an inability to do work or do usual daily activity.

An AE that is assessed as severe should not be confused with an SAE. Severity is **not** synonymous with "serious", which is based on patient/outcome, or action criteria usually associated with the events that pose a threat to a patient's life or functioning. An event is described as 'serious' when it meets one of the pre-defined outcomes as described in Section 9.1.2.

It is important to note that both AEs and SAEs can be assessed as severe.

9.2.2. Assessment of Causality (ICH Classification)

The causal relationship between an AE and APVO101 is defined as an established relationship between the occurrence of an AE and exposure to APVO101. Causality is assessed using the algorithm shown in Table 4: Causality Assessments of Reported Adverse Events.

Table 4: Causality Assessments of Reported Adverse Events

Unrelated	No temporal association to study product. An alternate etiology has been established. The event does not follow the known pattern of response to study product. The event does not reappear or worsen with re-challenge.
Possibly related	Reasonable temporal relationship to study product. The event is not readily produced by clinical state, environmental, or other interventions. The event follows a known pattern of response to the study product or as yet unknown pattern of response The event is not readily produced by clinical state, environmental, or other interventions. The event follows a known pattern of response to the study product or as yet unknown pattern of response
Probably related	There is a reasonable temporal association with the study product. The event is not readily produced by clinical state, environmental, or other interventions. The event follows a known pattern of response to the study product. The event decreases with de-challenge
Definitely related	There is a reasonable temporal relationship to the study product. The event is not readily produced by clinical state, environmental, or other interventions. The event follows a known pattern of response to the study product. The event decreases with de-challenge and recurs with re-challenge.

In accordance with ICH E2A and 21.CFR.312, the following definitions are used to assess causality (relatedness) of the adverse events:

Related: There is a reasonable possibility that the AE was caused by the product in question. The expression "reasonable possibility" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

Not-related / No relationship: The AE is clearly or most probably caused by other etiology such as the patient's underlying condition, therapeutic intervention or concomitant therapy, or the delay between the administration of the product and the onset of the AE is incompatible with a causal relation, or the AE started before the administration of the product.

Adverse events reported as definitely related, probably related, possibly related, will be considered as related AEs.

9.3. Description of Current Safety Profile for APVO101

Based on safety information collected from clinical trials involving APVO101, the safety profile is comparable to other recombinant factor IX products.

In study IB1001-01, all reported AEs assessed as definitely, probably and possibly related to APVO101 were considered to be related to APVO101 exposure and thus are defined as ADRs.

None of the reported ADRs were considered serious or severe.

Of the ADRs reported, only headache was reported more than once following administration of APVO101 to study subjects participating in IB1001-01; five events in 2.6% of study subjects. Headache has also been reported with other recombinant factor IX products.

Other ADRs (reported only once) included asthenia, injection site discomfort, influenza, anti- factor IX antibody positive (non-inhibitory), dysgeusia, lethargy, apathy, depression and pruritic rash.

Refer to the current APVO101 Investigator's Brochure for more details on regarding the safety profile for APVO101.

9.4. Adverse Event Reporting

The occurrence of AEs will be monitored throughout the clinical trial and will cover all participating subjects. Trial subjects and/or their parent or legal guardian will be provided with a 24-hour telephone number to contact trial personnel in case of an untoward reaction.

In the event of a reported occurrence of hypersensitivity and allergic reactions, anaphylaxis, and/or anaphylactic shock reactions, including but not limited to, symptoms of difficulty breathing, shortness of breath, swelling, hives, generalized urticaria, tightness of the chest, bronchospasm, laryngospasm, wheezing, hypotension, blurred vision, record these events on the APVO101 Serious Adverse Event Form and transmit the form within 24 hours to Medexus Pharmacovigilance using the following contact information:

[redacted]

The investigator must follow all AEs to resolution, or up to 30 days after the subject has completed the trial, whichever occurs first. The investigator must follow serious related AEs to resolution, or in the case of disability or incapacity, until the condition has stabilized. In the event that a patient does not complete the trial, efforts must be made to obtain information regarding all AEs, with a minimum follow-up of 30 days post-dosing.

9.5. Reporting of SAEs

The investigator will report all SAEs to the sponsor by telephone or e-mail within 24 hours of the investigator's knowledge of SAE occurrence. This will be followed by a fax or e-mail copy of the SAE Form. A written SAE report by the investigator to the sponsor (including medical summary of the SAE) must follow within **three days** of the investigator's knowledge of SAE occurrence.

All SAE reports should be made to Pharmacovigilance Department and the clinical trial medical monitor using the contact information indicated below:

Clinical Safety Surveillance	AND	Clinical Trial Medical Monitor
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]

9.6. Safety Data Monitoring

A Safety Monitoring Committee (SMC) will provide ongoing review of safety data during the trial. The SMC will be comprised of the sponsor Medical Monitor, the sponsor Safety Surveillance Officer, and one or more study investigators.

Following study initiation, the SMC will meet as needed to review ongoing safety data. The SMC will be responsible for assessing safety and monitoring overall conduct and integrity of the trial. In fulfilling these responsibilities, the SMC may make recommendations concerning continuation and/or stopping of the trial as it relates to safety and risk to the subject population.

If any one study subject develops an inhibitor (as determined by the central laboratory), regardless of the titer, the SMC will be informed. If a second study subject develops an inhibitor, the study will be placed on hold and the SMC, IRB/EC, FDA, and local regulatory authorities will be informed.

10. OTHER ASSESSMENTS

10.1. Assessment of Major and Target Joint(s)

Assessment of major joints (hips, knees, ankles, elbows, shoulders, wrists, etc.) will be performed by a physical therapist or the investigator (at Screening, 50 ED and 100 ED visits) and will include evaluation of joint swelling, muscle atrophy, range of motion, and presence/absence of flexion contracture.

A target joint is defined as a joint with three or more bleeds within a 3-month period.

The number of target joints will be documented before (at Screening) and after APVO101 prophylaxis treatment (at 50 ED and 100 ED visits; see Table 1).

Assessment of target joint(s) will be performed by a physical therapist or the investigator (at Screening, 50 ED and 100 ED visits) and will include evaluation of joint swelling, muscle atrophy, range of motion, and presence/absence of flexion contracture.

10.2. Subject-reported Assessments

Subject diaries will be maintained by all subjects and/or their parent or legal guardian and evaluated by site investigators during follow-up visits.

Subjects and/or their parent or legal guardian will record details of each bleeding episode, including the reason for bleeding, symptoms and signs associated with the bleed, dose amount required to control bleeding, administration of each dose, and outcome of the treatment of the bleed.

Subjects and/or their parent or legal guardian will record time, date, and amount of each dose administered.

10.3. Mutation Genotyping

Blood sampling for DNA extraction to determine molecular diagnosis of factor IX gene mutation will be completed at the 12 ED Visit. Note, for patients below 10 kg this may be done at any time during the study when blood volumes allow.

If a subject has previously been genotyped and a report documenting the type of mutation is available, this test will not be performed. A copy of the report will be collected as part of clinical monitoring.

11. STATISTICAL ISSUES IN TRIAL DESIGN

11.1. Sample Size Calculation

No formal sample size calculation was performed given that all planned analyses are descriptive in nature. Up to 22 subjects will be enrolled to ensure that at least 15 to 20 evaluable subjects complete all phases of the study. The target sample size is intended to enhance the existing pediatric sample size to be compliant with the EMA regulatory guidelines and the FDA post-marketing requirement for APVO101 (see Section 3.3).

11.2. Clinical Trial Endpoints

11.2.1. PK Endpoints

All PK endpoints will be calculated based on the factor IX concentration levels. The actual time of sampling and actual dose will be used for the dose/time dependent PK endpoints. The PK endpoints listed below will be calculated with and without baseline correction.

Baseline correction will be performed using the subtraction method such that all post-infusion concentrations will have the pre-infusion concentration subtracted. All negative baseline-corrected concentrations will be set to zero prior to the calculation of PK parameters.

The following PK endpoints will be calculated:

- Maximum post-infusion plasma concentration (C_{max})
- Incremental recovery
- *In vivo* recovery (IVR)
- 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 (MRT)
- Elimination rate constant (λ_Z)
- Terminal half-life ($t_{1/2}$)
- Clearance (CL)
- Volume of distribution at steady-state (Vd_{ss})

11.2.2. Efficacy Endpoints

The following efficacy endpoints will be evaluated for the Treatment and Continuation phases of the study:

Primary Efficacy Endpoint:

- Annualized bleeding rate (ABR) while on prophylaxis to prevent bleeding episodes.

Secondary Efficacy Endpoints:

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

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

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

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

Exploratory Efficacy Endpoints:

The following endpoints will be calculated for surgical procedures (if applicable):

- Surgeon assessment of estimated blood loss at time of surgery
- Surgeon assessment of post-surgery blood loss (at 12-hour and 24-hour post-surgery time points)

11.2.3. Safety Endpoints

The following safety endpoints will be evaluated:

- Adverse events
- Inhibitory factor IX antibodies
- Non-inhibitory factor IX antibodies
- Anti-CHOP antibodies
- Thrombogenicity markers

11.3. Interim Analyses

When a sufficient number of subjects completes their 50 ED visit, available PK and safety/efficacy data (for at least 50 ED) will be included for data analysis of an integrated pediatric report required for US post-marketing requirement.

11.4. Planned Method of Analyses

A formal statistical analysis plan (SAP) will be prepared prior to the execution of any statistical analyses and will provide additional details on the planned methods for analysis.

11.4.1. PK Analysis

No formal statistical comparisons of PK endpoints are planned, however all PK parameters calculated with and without baseline correction, both for initial and repeat PK assessments will be summarized through the use of descriptive statistics, including the mean, median, geometric mean, standard deviation, range and 95% confidence interval for the mean.

Listings will be prepared for individual concentrations over time as well as the PK parameters by subject.

11.4.2. Efficacy Analysis

No formal statistical comparisons are planned. Descriptive summaries and listings of all treatment and continuation phase efficacy endpoints, as well as the surgeon's assessment of estimated blood loss during and after surgery, will be provided.

The annualized bleeding rate will be calculated and summarized, including the median, interquartile range and the 95% exact confidence interval for the median, assuming that the rates follow a Poisson distribution.

11.4.3. Safety Analysis

All AEs and SAEs will be coded using MedDRA. The analyses of AEs will include descriptive statistics and will be summarized through the use of frequency tables overall and by type (AE or SAE), body system and preferred term, intensity and relationship of events to treatment.

Summary statistics for laboratory tests (including non-inhibitory and inhibitory factor IX antibody levels and anti-CHOP results) over time will be provided.

Levels of thrombogenic markers will be summarized by subject and evaluated against criteria for this measurement.

The incidence of non-inhibitory factor IX antibodies and incidence of anti-CHOP antibodies will be calculated along with corresponding 95% exact confidence intervals using the binomial distribution.

12. REGULATORY AND ETHICAL ISSUES

12.1. Declaration of Helsinki

The investigator shall ensure that this trial is conducted in accordance with the "Declaration of Helsinki" (Version 6, October 2008).

12.2. Informed Consent / Assent

The investigator (or his/her representative) will obtain written informed consent, or assent where applicable, from prospective trial candidates/legal guardians before enrolment or the performance of any trial procedures. The proper completion of consent/assent forms will be monitored by sponsor personnel and the original signed informed consent form(s) (ICF) and assent form will be maintained in the Investigator site file.

A copy of the signed ICF or assent form must be given to the subject and/or their parent or legal guardian. If the ICF or assent form is revised, all trial subjects and/or their parent or legal guardian who are ongoing in the trial must be re-consented to the current IRB/EC-approved version of the ICF/assent form at their next trial visit.

12.3. Institutional Review Board (IRB) / Ethics Committee (EC)

Before the start of the trial, the Investigator's Brochure, the protocol, proposed ICF/assent form, subject compensation (if any), Medexus-approved trial materials and advertisements, and any other written information to be provided to the subject and/or their parent or legal guardian, will be submitted to a properly constituted IRB/ EC for review. Medexus must receive a copy of the written approval from the IRB/EC for all of the above applicable documents prior to recruitment of subjects into the trial and shipment of APVO101.

The IRB/EC must provide written approval for all amendments to any of the above documents prior to implementation of these amendments at the investigational site. The investigator is obliged to report SAEs, as well as any unanticipated problems, to the IRB/EC in addition to other information as required by the IRB/EC.

The names (or title, if IRB/EC procedures prohibit publishing of names) and associated backgrounds of the members of IRB/EC (to assist in assuring that the board membership is properly constituted and operates according to required regulations) will be given to the sponsor (Medexus) prior to the start of the trial along with a signed and dated statement stating that the protocol and Informed Consent Form and, where applicable, any other document listed above, have been approved by them.

All correspondence between the investigator and the IRB/EC will be available for review by the sponsor (or designate), Contract Research Organization (CRO) personnel, and the applicable regulatory authorities.

12.4. Documentation Required Prior to Trial Initiation

The investigator (or designate) is responsible for forwarding the following documents to Medexus for review prior to trial initiation:

- Signed protocol signature page, form FDA 1572 (or equivalent, depending on local regulatory requirements), financial disclosure form, debarment certification statement, Clinical Trial Agreement, and any other required regulatory documents.
- Copy of IRB/EC-approved ICF/assent form.
- Copy of the written IRB/EC approval for the protocol, Investigator's Brochure, informed consent form(s), subject compensation (if any), any trial materials and advertising, and any other written information to be provided to the subject and/or their parent or legal guardian.
- Current Curriculum Vitae and a photocopy of medical license (if applicable) of the principal investigator, co/sub investigators and other site personnel as required by the Sponsor/CRO.
- Written statement that the IRB/EC is properly constituted and operates according to required regulations. Investigators participating in this study, if IRB/EC members, should state in writing that they have abstained from voting in regard to this protocol.
- Laboratory normal ranges and documentation of laboratory certification.
- Signed site contract agreement.

12.5. Subject Confidentiality

The investigator must ensure the anonymity of each subject is maintained at all times. Subjects should only be identified by their initials and Subject Trial ID (enrolment) number on the CRF, or on any other trial documents provided to the Sponsor or their designate(s). Any documents that identify the subject should be kept in strict confidence by the principal investigator.

Based on ICH GCP guidelines and regulatory requirements, the investigator is required to allow authorized personnel of Medexus (or its designate), the IRB/EC, and members of the appropriate regulatory authorities to review subject's files that are related to APVO101-903. Subjects and/or their parent or legal guardian must be informed that his/her records may be reviewed by Medexus, its designate(s), the IRB/EC and the appropriate regulatory authorities through direct access to the subject's original medical records.

13. ADMINISTRATIVE AND LEGAL REQUIREMENTS

13.1. Sponsorship

This clinical trial is sponsored by Medexus Pharma Inc., d.b.a Aptevo BioTherapeutics, LLC located at 29 N Wacker Drive, Suite 704, Chicago, IL 60606, USA.

The APVO101 drug substance is manufactured for Medexus by [redacted]

The APVO101 drug product is formulated for Medexus by [redacted]

The final APVO101 drug product packaging and labeling for this clinical trial is performed for Medexus by [redacted]

13.2. Protocol Amendments

Protocol amendments will only be made by Medexus. Any change to the protocol must be made in the form of a formal amendment to the protocol and must be approved in writing by the principal investigator, the sponsor, and the IRB/EC and regulatory agencies (where applicable) prior to implementation. The investigator must receive written IRB/EC approval for all protocol amendments prior to implementing protocol amendments at the trial site, and the investigator must send a copy of any IRB/EC correspondence and all approval/disapproval letters from the IRB/EC to Medexus.

13.3. Deviations from the Protocol

The investigator agrees to conduct the clinical trial in compliance with the protocol agreed to by Medexus and approved by the IRB/EC. The investigator and Medexus shall sign the protocol to confirm this agreement.

The investigator will not deviate from this protocol for any reason without prior approval of the sponsor and the IRB/EC, except in cases of medical emergencies. The investigator may deviate from the protocol without the prior approval of the IRB/EC or Medexus only when the deviation is necessary to eliminate an apparent immediate hazard to the subjects. In that event, the investigator must notify the IRB/EC and Medexus in writing as soon as possible and no more than five working days after the deviation is implemented. The investigator shall document and explain any deviation from the approved protocol.

13.4. Source Documentation and Storage

The principal investigator will maintain the following information:

- Medical history/physical condition of the trial subject before involvement in the trial sufficient to verify protocol entry criteria.

- Dated and signed notes on the day of entry into the trial including the trial number, the drug being evaluated, subject trial ID number assigned, and a statement that informed consent/assent form was obtained, noting the time the consent was obtained.
- Dated and signed notes from each trial subject visit that refer to the protocol or CRFs for further information, if appropriate (i.e., for specific procedures and exams).
- Subject diary page(s) following the assessment visit.
- The investigator will assess each abnormal lab result as clinically significant or not clinically significant. For clinically significant results, a brief explanation will be written on the laboratory report. These assessments will be noted on the laboratory report source document and signed and dated on the date of the investigator's review.
- Notes regarding concomitant medications taken during the trial (including start and stop dates).
- Source documents regarding adverse events occurring during the trial including date of onset and cessation, seriousness, severity, causality, action taken and related concomitant medications.
- Trial subjects' condition upon completion, or withdrawal from, the trial.
- All communications with the IRB/EC responsible for the trial.
- Drug accountability records.
- Any other records as required by the Sponsor/designate, the IRB/EC or the regulatory authorities.

The investigator must arrange for the retention of the subject identification codes according to local regulatory requirements. Subject files and other source data must be securely stored and kept for the maximum time permitted by the hospital, institution or private practice but not less than local regulatory requirements. Archival data may be held on microfiche or electronic record, provided that a backup exists, and that hard copy can be obtained from it if required. If source documents are to be destroyed as per hospital or local regulatory policy, the investigator is requested to contact the sponsor.

Records from the trial that identify the subject will be confidential except that they may be given to and inspected by the sponsor of the trial or designate(s), the IRB/EC, the Food and Drug Administration, other government agencies as appropriate, and will not otherwise be released except as required by law. All information provided to the investigator by the sponsor is to be considered confidential unless otherwise stated.

13.5. Data Forms

Detailed specifications for data management will be outlined in a Data Management Plan (DMP) that will be finalized before data collection is initiated. The DMP is a dynamic document that will be updated throughout the conduct of the study, as needed, to ensure the accuracy and quality of the database.

Designated study site personnel will record study data into electronic CRFs within the study electronic data capture (EDC) system. The investigator is responsible for the accuracy of the data entered into the CRFs and will be required to electronically sign the forms to indicate agreement with the recorded data.

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they can only be accessed by authorized staff.

13.6. Monitoring

At the time the trial is initiated, monitors from the sponsor/CRO will thoroughly review the protocol and data forms with the investigators and their staff. During the trial, the monitors will be available to discuss by telephone, e-mail, or in person (during site visits), questions regarding study criteria, adverse reactions, removal of subjects from the trial, conduct of the trial and other clinical trial matters. Monitors from the sponsor/CRO will visit at the initiation of the trial, during the trial and at the completion of the trial. At the time of each monitoring visit, the monitors will check the case report forms of the subjects to ensure that all items have been completed, that the data are accurate and obtained in the manner specified in the protocol and that data recorded on the data forms for the trial agree with medical records at the site. The monitors will also check for general protocol and regulatory compliance by subjects and site personnel.

13.7. Quality Control and Quality Assurance

Medexus Quality Assurance department (or authorized representatives) may conduct onsite audits of all aspects of the clinical trial prior to, during the trial, or after the trial has been completed. The clinical trial may also be inspected by regulatory authorities or the IRB/EC to verify that the trial is being or has been conducted in accordance with protocol requirements, GCP, as well as the applicable regulatory requirements.

13.8. Publication Policy

Data arising from this trial are the sole property of the sponsor of the trial, Medexus. The sponsor must provide written, prior agreement to any publication based, in whole or in part, on data from this trial. All proposed abstracts, manuscripts or presentations from the study must be provided to Medexus for review at least 60 days prior to submission for publication/presentation. Any information identified by Medexus as confidential must be deleted prior to submission.

The Publication Policy applicable to this protocol is the one agreed upon and described in the Clinical Trial Agreement between Medexus and the principal investigator.

14. REFERENCES

1. Ingerslev J. Pharmacovigilance studies in haemophilia. Haemophilia. 2007;13:121-123.
2. Shord SS, Lindley CM. Coagulation products and their uses. Am J Health Syst Pharm, 2000;57(15):1403–1417.
3. Srivastava A, et al. World Federation of Hemophilia, Guidelines for the Management of Hemophilia, Haemophilia 2013;19:e1–e47.
4. Giangrande P. Hemophilia B: Christmas disease. Expert Opin in Pharmacother. 2005;6(9):1517-1524.
5. BENEFIX® [Coagulation Factor IX (Recombinant)] US Prescribing Information. Pfizer. 2012.
6. RIXUBIS® [Coagulation Factor IX (Recombinant)] US Prescribing Information. Baxter Healthcare Corporation. 2014.
7. ALPROLIX® [Coagulation Factor IX (Recombinant), Fc Fusion Protein]. US Prescribing Information. Biogen Idec, Inc. 2014.
8. IDELVION® [Coagulation Factor IX (Recombinant), Albumin Fusion Protein]. US Prescribing Information. CSL Behring LLC. 2018.
9. REBINYN® [Coagulation Factor IX (Recombinant), GlycoPEGylated]. US Prescribing Information. Novo Nordisk Inc. 2017.
10. Di Scipio RG, Hermodson MA, Yates SG, Davie EW. A comparison of human prothrombin, factor IX (Christmas factor), factor X (Stuart factor), and protein S. Biochemistry. 1977;16(4):698-706.