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PHASE OF DEVELOPMENT: 1/2a

PROTOCOL TITLE: A Phase 1/2a, Open-Label, Dose-Escalation Study to Determine the Safety, Tolerability, and Pharmacokinetics of a Single Intravenous Injection of rFVIIIFc-VWF-XTEN (BIVV001) in Previously Treated Adults with Severe Hemophilia A

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Bioverativ Therapeutics, Inc.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. SYNOPSIS

Protocol Title	A Phase 1/2a, Open-Label, Dose-Escalation Study to Determine the Safety, Tolerability, and Pharmacokinetics of a Single Intravenous Injection of rFVIIIFc-VWF-XTEN (BIVV001) in Previously Treated Adults with Severe Hemophilia A
Protocol Number	Protocol 242HA101
Version Number	6.0
Name of Study Treatment	Recombinant coagulation factor VIII Fc - von Willebrand factor - XTEN fusion protein (rFVIIIFc-VWF-XTEN; BIVV001)
Study Phase	1/2a
Study Indication	Severe Hemophilia A
Study Rationale	Severe hemophilia A (<1 IU/dL [<1%] endogenous factor VIII [FVIII] activity level) accounts for approximately 30% to 50% of all cases of hemophilia A. The World Health Organization, the World Federation of Hemophilia, and other international expert consensus groups recommend FVIII prophylactic therapy to prevent bleeding and related joint and musculoskeletal disease [Berntorp 1995; Berntorp 2003; Srivastava 2013; National Hemophilia Federation (NHF) 2016], and FVIII prophylaxis is considered the standard of care for patients with severe hemophilia A. Prior to the introduction of recombinant coagulation factor VIII Fc (rFVIIIFc), FVIII products were generally administered every 2 to 3 days due to the short half-life ($t_{½}$) of the protein: approximately 10 to 12 hours in adults [Fijnvandraat 1997; White 1997; Tarantino 2004; Blanchette 2008]. The longer mean $t_{½}$ of rFVIIIFc — 19.7 hours (95% confidence interval: 17.4, 22.0) in adults [Eloctate USPI 2017], which allows for less frequent administration: every 3 to 5 days. Nevertheless, there is still a need for further improvement in FVIII therapy via the development of products with longer half-life, as the burden of a demanding treatment regimen remains an obstacle to adoption of and adherence to prophylaxis. Next-generation extended half-life (EHL) FVIII products — which could reduce the frequency of bleeding episodes with less frequent administration due to their prolonged periods of prophylactic coverage — would potentially address these challenges and in turn could improve the quality of life for hemophilia patients [Collins 2009].

BIVV001 (rFVIIIFc-VWF-XTEN), designed to be a next-generation EHL blood clotting FVIII, is a recombinant fusion protein consisting of single chain FVIII, the Fc domain of human immunoglobulin G1, the FVIII-binding D′D3 domain of von Willebrand factor (VWF), and 2 XTEN polypeptide linkers. BIVV001 is the first rFVIII engineered to be independent of VWF, and has been shown to have a longer half-life compared with current FVIII and rFVIII products in nonclinical studies.

Study Objectives and Endpoints

The primary objective is to assess the safety and tolerability of a single intravenous (IV) dose of BIVV001 in adult previously treated patients (PTPs) with severe hemophilia A.

The primary endpoints are as follows:

- The occurrence of adverse events (AEs).
- The occurrence of clinically significant abnormalities in laboratory tests, including development of inhibitors (neutralizing antibodies directed against FVIII) as determined via the Nijmegen-modified Bethesda assay.

The secondary objective is to characterize the pharmacokinetics (PK) of BIVV001 after a single IV administration compared with the PK of Advate®, with FVIII activity determined by the one-stage (activated partial thromboplastin time [aPTT]) clotting assay.

The secondary endpoints are PK parameters, including but not limited to the following: maximum activity (C_{max}); half-life ($t_{½}$); clearance; volume of distribution at steady state (V_{ss}); area under the concentration-time curve from time 0 to infinity (AUC_{∞}); mean residence time (MRT); incremental recovery (IR); time to 1% above baseline for FVIII activity.

Study Design

This is a Phase 1/2a, open-label, dose-escalation, multicenter study designed to evaluate the safety, tolerability, and PK of a single IV dose of BIVV001 in PTPs with severe hemophilia A.

Subjects will be dosed with a single IV dose of Advate followed by a PK sampling period. After a brief washout period, each subject will be administered a single dose of BIVV001 followed by a PK sampling period. Subjects will also undergo safety observation for 28 days following BIVV001 administration, which includes inhibitor assessments 14 and 28 days after BIVV001 dosing.

Two BIVV001 doses will be evaluated in this study: 25 IU/kg single dose (low-dose cohort) and 65 IU/kg single dose (high-dose cohort).

A step-wise dosing and dose-escalation procedure will be utilized to minimize the potential of adverse reactions in multiple subjects:

1. For the low-dose cohort, data collected for inhibitor test results and other available safety assessments through 28 days post-BIVV001 dose for Subject 1 must be reviewed before permitting administration of BIVV001 to Subject 2, and the same data through 28 days post-BIVV001 dose must be reviewed before permitting administration of BIVV001 to Subject 3. After BIVV001 administration to Subject 3, data will be reviewed for inhibitor test results and other available safety assessments through 14 days post-BIVV001 dose, before permitting administration of BIVV001 to Subject 4 [Abbas 2007]. For Subjects 4 through 8 of this cohort, an interval of at least 72 hours must elapse between BIVV001 dose administrations to successive subjects.

2. Before proceeding to the high-dose cohort, the Sponsor and the Data Safety Monitoring Committee (DSMC) will review available data obtained from the low-dose cohort to determine whether it is appropriate to begin administration of the higher BIVV001 dose.

3. For the high-dose cohort, data collected for inhibitor test results and other available safety assessments through 28 days post-BIVV001 dose for Subject 1 must be reviewed before permitting administration of BIVV001 to Subject 2, and the same data through 28 days post-BIVV001 dose must be reviewed before permitting administration of BIVV001 to Subject 3. After BIVV001 administration to Subject 3, data will be reviewed for inhibitor test results and other available safety assessments through 14 days post-BIVV001 dose, before permitting administration of BIVV001 to Subject 4 [Abbas 2007]. For Subjects 4 through 10 of this cohort, an interval of at least 96 hours must elapse between BIVV001 administrations to successive subjects.

Study Locations	Approximately 10 sites in North America and Asia.
Number of Planned Subjects	A total of approximately 18 adult males will be enrolled and treated.
Study Population	Adult male subjects (18 to 65 years of age) with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII) who have had at least 150 exposure days (EDs) to the FVIII product.

	Detailed entry criteria for each cohort are described in Section 8.
Treatment Groups	Approximately 8 subjects in the low-dose cohort (Advate 25 IU/kg single dose and BIVV001 25 IU/kg single dose). Approximately 10 subjects in the high-dose cohort (Advate 65 IU/kg single dose and BIVV001 65 IU/kg single dose).
Duration of Treatment and Follow-up	The total time on study for each subject in the low- and high-dose cohorts will range from approximately 60 to 156 days, depending on the length of Screening Period and the cohort to which the subject is assigned. • Up to 28 days for screening and washout of prestudy FVIII therapy prior to Advate dosing (this period may be extended up to 120 days with prior Sponsor approval). If the Screening Period extends beyond 56 days, screening assessments must be repeated as specified in Table 1 prior to dosing with Advate. • At least 3 days (low-dose cohort) of Advate PK sampling/washout following Advate dose administration • At least 4 days (high-dose cohort) of Advate PK sampling/washout following Advate dose administration • 28 days of safety observation (which includes 10 to 14 days of BIVV001 PK sampling) following BIVV001 dose administration.

2. LIST OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASA	Acetylsalicylic acid
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC_{∞}	area under the concentration-time curve from time 0 to infinity
BU	Bethesda units
BUN	blood urea nitrogen
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
C_{max}	maximum activity
CRF	case report form
DHA	Directions for Handling and Administration
DLT	dose-limiting toxicity
DSMC	Data Safety Monitoring Committee
ED	exposure day
EHL	extended half-life
EMA	European Medicines Agency
EOS	end of study
ET	early termination
FVIII	factor VIII
γGT	gamma-glutamyl transferase
GCP	Good Clinical Practice
HBV	hepatitis B virus
Hct	hematocrit
HCV	hepatitis C virus
HemA	FVIII-deficient (mouse strain)
Hgb	hemoglobin
HIV	human immunodeficiency virus
[redacted]	[redacted]
IB	(BIVV001) Investigator Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IGF-1	insulin-like growth factor type 1
IgG1	immunoglobulin G1
INR	international normalized ratio
IR	incremental recovery
IRT	Interactive Response Technology

IU	international units
IV	intravenous(ly)
MASAC	Medical and Scientific Advisory Council
MedDRA	Medical Dictionary for Regulatory Activities
MRT	mean residence time
NHF	National Hemophilia Foundation
NOAEL	no-observed adverse effect level
NSAID	non-steroidal anti-inflammatory drug
PK	pharmacokinetics
PT	prothrombin time
PTE	pretreatment event
PTP	previously treated patient
RBC	red blood cell
rFVIII	recombinant coagulation factor VIII
rFVIIIFc	recombinant coagulation factor VIII Fc
rFVIIIFc-VWF-XTEN	recombinant coagulation factor VIII Fc – von Willebrand factor – XTEN fusion protein (BIVV001)
rhGh	recombinant human growth factor
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
TAT	thrombin anti-thrombin
ULN	upper limit of normal
USPI	United States Prescribing Information
V_{ss}	volume of distribution at steady state
VWF	von Willebrand factor
VWF:RCo	von Willebrand factor ristocetin cofactor
WBC	white blood cell
WHO	World Health Organization

3. SPONSOR INFORMATION

This study is sponsored by Bioverativ Therapeutics Inc. (Bioverativ). Refer to the Study Reference Guide for complete information for all study contacts.

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For urgent medical issues in which the study's Medical Director should be contacted, please refer to the Study Reference Guide for complete contact information.

Bioverativ may transfer any or all of its study-related responsibilities to IQVIA, contract research organizations, and/or other third parties; however, Bioverativ retains overall accountability for these activities.

4. INTRODUCTION

In this study, approximately 18 males (18 to 65 years of age, inclusive) with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous factor VIII [FVIII]) will be administered a single intravenous (IV) dose of 25 IU/kg or 65 IU/kg BIVV001 (rFVIIIFc-VWF-XTEN) at approximately 10 sites in North America and Asia to evaluate the safety and tolerability of BIVV001. Additionally, this study will evaluate the pharmacokinetics (PK) of BIVV001 (single dose) and compare it to the PK of single-dose administration of the commercially available recombinant FVIII (rFVIII) product Advate®.

4.1. Overview of Hemophilia A

Hemophilia A is an X-chromosome linked bleeding disorder that occurs predominantly in males, and is characterized by a functional FVIII deficiency caused by a variety of mutations occurring in the gene that encodes FVIII [Furie and Furie 1990; Graw 2005]. The worldwide prevalence of hemophilia A is estimated to be 1 in 10,000, whereas the worldwide incidence is approximately 1 in 5,000 male births [Roosendaal and Lafeber 2003]. Hemophilia A appears to be equally distributed around the world [World Federation of Haemophilia 2011; Skinner 2012]. The severity of the disease is characterized by the endogenous level of FVIII calculated in plasma. Severe hemophilia A (<1% endogenous FVIII activity level; <1 IU/dL) accounts for approximately 30% to 50% of all cases of hemophilia A [Aznar 2009; Centers for Disease Control and Prevention (CDC) 2011; United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) 2011].

Individuals with severe hemophilia experience frequent bleeding episodes into major joints, soft tissue, and muscle, either spontaneously or following trauma. Signs and symptoms of hemophilia A include joint swelling, joint and muscle pain, as well as mucosal, gastrointestinal, and post-circumcision bleeding. Repeated bleeding episodes can lead to debilitating long-term complications, including hemophilic arthropathy from bleeding into the joints. The disease can be acutely life threatening; intracranial hemorrhage can result in disability and death, and is the leading cause of hemorrhagic death in individuals with hemophilia [Witmer 2011]. Another severe complication is the development of target joints from inflammation due to prior bleeding. Patients are more susceptible to recurrent bleeding into that same joint, ultimately leading to disabling arthropathy. Significant effects on physical/psychosocial well-being, quality of life, and financial burden have been reported in patients with severe hemophilia [Lee 2010].

4.2. Current Therapies for Hemophilia A

Currently, no cure is available for hemophilia A. Current standard of care focuses on replacement therapy with plasma-derived FVIII or rFVIII products. Although FVIII and rFVIII products have similar efficacy and safety profiles, rFVIII products are more commonly used because they are not associated with the theoretical risk of pathogen transmission.

The FVIII treatment of hemophilia A can be episodic or prophylactic. Clinical studies have shown that routine prophylactic therapy is superior in delaying/preventing the development of arthropathy, as well as in controlling bleeding frequency [Nilsson 1992; Aledort 1994; Manco-Johnson 2007]. For these reasons, the World Health Organization (WHO), the World Federation of Hemophilia, and other international expert consensus groups recommend FVIII prophylaxis to prevent bleeding and reduce secondary joint and musculoskeletal disease [Berntorp 1995; Berntorp 2003; Srivastava 2013; National Hemophilia Federation (NHF) 2016]. As prophylactic regimens were initially developed, a target trough of 1% factor activity was adopted based on the observation of a significantly decreased frequency of bleeding in moderate hemophilia A patients, who have factor activity levels of 1% to 5% of the endogenous FVIII level.

For effective prophylaxis, FVIII products with protein half-lives ($t_{½}$) of 10 to 12 hours are generally administered every 2 to 3 days in adults [Fijnvandraat 1997; White 1997; Tarantino 2004; Blanchette 2008]. Newer extended half-life (EHL) PEGylated FVIII products have mean $t_{½}$ ranging from 14 to 19.6 hours in adults; these include glycoPEGylated FVIII (N8-GP), Cys variant-PEGylated FVIII (BAY 94-9027), and amino group-PEGylated FVIII (BAX855) [Tiede 2013; Coyle 2014; Konkle 2015]. The recombinant FVIII-Fc fusion protein (rFVIIIFc; Eloctate®), has a longer mean $t_{½}$ of 19.7 hours (95% CI: 17.4, 22.0) in adults [Eloctate United States Package Insert [USPI] 2017], which allows for less frequent administration: every 3 to 5 days.

Nevertheless, there is still a need for further improvement. FVIII administration is challenging, particularly in children with hemophilia A, due to the requirement for venous access, dosing compliance due to time commitment, and the cost associated with frequent administration [Blanchette 2008]. Additionally, children have higher body-weight-normalized clearance (CL) and shorter half-life, necessitating more frequent injections. Even with the EHL FVIII products that are currently available, the burden of a demanding regimen remains an obstacle to adoption of and adherence to prophylaxis. Products with even longer half-life would offer the opportunity for reduced time below threshold FVIII activity levels at which there may be an increased risk of bleeding events [Collins 2009].

BIVV001 (rFVIIIFc-VWF-XTEN) is a recombinant fusion protein consisting of single chain FVIII, the Fc domain of human immunoglobulin G1 (IgG1), the FVIII-binding D′D3 domain of von Willebrand factor (VWF), and 2 XTEN linkers. It is believed that the plasma half-life of FVIII is prolonged by its interaction with VWF. All current EHL rFVIII products interact with VWF and have comparable circulating half-lives, consistent with upper limits on the half-life of rFVIII variants owing to the approximate 15-hour half-life of endogenous VWF [Pipe 2016]. BIVV001 is the first rFVIII engineered to be independent of VWF, theoretically extending its half-life. Nonclinical studies of BIVV001 have demonstrated that its half-life is significantly prolonged compared with current FVIII products.

4.3. Profile of Previous Experience With BIVV001

See the BIVV001 Investigator Brochure (IB) for detailed information on relevant nonclinical studies.

4.3.1. Nonclinical Experience

The PK of BIVV001 have been characterized in FVIII-deficient (HemA) mice, normal Sprague Dawley rats, and normal Cynomolgus monkeys. The results from these studies demonstrated that the half-life of BIVV001 was 2.8-fold, 3.6-fold, and 4.1-fold longer than that of Advate in each of these species, respectively.

Nonclinical efficacy of BIVV001 has been evaluated using 2 bleeding models in HemA mice: a tail clip model to evaluate acute efficacy and a tail vein transection model to evaluate prophylactic efficacy. In the tail clip study, the observed in vivo activity of BIVV001 was comparable to that of Advate, and both demonstrated significantly decreased blood loss compared to the vehicle control. In the tail vein transection study, BIVV001 demonstrated a 3-fold increase in its duration of protective activity compared to that observed for Advate, which is consistent with the prolonged half-life of BIVV001 observed in nonclinical PK studies.

In 4-week, repeated-dose toxicology studies in normal Sprague Dawley rats and normal Cynomolgus monkeys, no unexpected toxicity findings were observed for BIVV001. No adverse findings were observed that were directly attributed to BIVV001 administration. The no-observed adverse event level (NOAEL) was determined to be BIVV001 750 IU/kg, which was the highest dose level administered IV in these studies. Adverse findings were observed in monkeys; however, these were directly related to antibody formation to BIVV001 and cross-reactivity with endogenous FVIII, resulting in acquired hemophilia. The development of antibodies is an expected finding, as BIVV001 is a foreign protein to monkeys.

4.3.2. Clinical Experience

This drug has not yet been evaluated in humans.

4.4. Study Rationale

BIVV001 has been designed to be a next-generation EHL blood clotting FVIII. This first-in-human study will evaluate the safety and tolerability of a single IV dose of BIVV001 in subjects with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII). In addition, this study will provide data on the PK of this drug compared with that of Advate, which was chosen as a comparator because it is a commonly prescribed rFVIII replacement product. The results of this study will inform the design of Phase 3 clinical studies.

BIVV001 has not yet been evaluated in humans. As described in Section 4.3.1, nonclinical studies have shown that BIVV001 has an EHL compared with current FVIII products. Additionally, in silico tools were utilized in the design and preparation of BIVV001 to assess and reduce the immunogenic potential of this fusion protein [Chhabra 2016].

BIVV001 was engineered to include an rFVIIIFc containing a B-domain deleted human FVIII covalently linked to the Fc domain of human IgG1. The rFVIIIFc binds to the neonatal Fc receptor, utilizing a naturally occurring pathway by which the receptor binds the Fc region of IgG1 and protects immunoglobulins from lysosomal degradation. The rFVIIIFc fusion thereby allows for longer plasma half-life than endogenous FVIII. The fusion of Fc to human FVIII

utilized a proven approach for increasing the half-life of therapeutic proteins, including several approved drugs [Jazayeri 2012; Wu 2014]. Additionally, the rFVIIIFc in BIVV001 has been appended to the D′D3 domain of VWF, which not only provides protection and stability to FVIII, but also prevents FVIII interaction with endogenous VWF, thus overcoming the limitation on FVIII half-life imposed by VWF [Saenko and Scandella 1995; Yee 2014; Lenting 2016]. The D′D3 domain has not been reported to interact with other targets.

Finally, BIVV001 also includes 2 XTEN linkers (unstructured polypeptides): the first is located in the B-domain region of FVIII (connecting the heavy and light chains of FVIII), while the second is located between the D′D3 and Fc domains. These XTEN linkers are designed to extend the half-life of the fusion protein and reduce clearance [Schellenberger 2009], which has been demonstrated in studies where XTEN linkers have been joined to other protein drugs. An allometric scaling analysis of Exenatide-XTEN showed that the fusion of XTEN to the compound would result in a $t_{½}$ of 139 hours in humans versus 2.4 hours for Exenatide alone [Schellenberger 2009; Byetta USPI 2015]. These analyses were confirmed in a Phase 1, placebo-controlled study of Exenatide-XTEN single dose in 52 patients with type 2 diabetes mellitus: the average $t_{½}$ of Exenatide-XTEN was 128 hours in these patients [Cleland 2012]. In a study conducted in rats, the half-life of T-20 — an anti-retroviral peptide indicated for patients with human immunodeficiency virus (HIV) — was increased nearly 20-fold when fused to XTEN linkers [Ding 2014]. In a study of 50 adult humans with growth hormone deficiency, the half-life of a recombinant human growth factor (rhGH) fused with XTEN was 30- to 60-fold longer than that previously observed for rhGH alone. Moreover, efficacy responses (assessed via observation of ample levels of insulin-like growth factor type 1 [IGF-1]) persisted for a full month after a single dose of rhGH-XTEN was administered; in contrast, rhGH typically must be administered daily to maintain efficacy [Yuen 2013]. In a study of 68 pediatric patients with growth hormone deficiency, a single dose of rhGH-XTEN resulted in a sustained IGF-1 response for up to 1 month [Moore 2016].

Nonclinical single-dose PK studies demonstrated BIVV001 half-life that was approximately 3-fold longer than that of Advate in all species tested. This first-in-human study of BIVV001 is being conducted to evaluate the safety and tolerability of a single intravenous injection of BIVV001 at either 25 IU/kg or 65 IU/kg and assess whether BIVV001 demonstrates a similar half-life prolongation compared with Advate in adult males with severe hemophilia A.

4.5. Rationale for Dose and Schedule Selection

There will be 2 dose cohorts in this study:

- Low-dose cohort: Approximately 8 subjects will receive a single IV dose of Advate 25 IU/kg followed by a single IV dose of BIVV001 25 IU/kg
- High-dose cohort: Approximately 10 subjects will receive a single IV dose of Advate 65 IU/kg followed by a single IV dose of BIVV001 65 IU/kg

The low-dose level for this study is based on nonclinical study results for BIVV001 and clinical and nonclinical results for marketed FVIII products, including rFVIIIFc (Eloctate).

The high-dose level is determined by the upper limit of the physiological plasma FVIII activity level of 150 IU/dL in healthy subjects and taking into account an anticipated incremental recovery (IR) of 2 IU/dL per IU/kg (based on values typically observed for FVIII products, including rFVIIIFc). Data from nonclinical studies have shown a BIVV001 procoagulation capacity per IU similar to those of other FVIII products.

The 2 dose levels considered for this study are expected to approximately bracket the therapeutic dose range. The physiological plasma FVIII activity level in healthy subjects is between 50 and 150 IU/dL. The low dose (25 IU/kg) for this study is expected to provide a peak activity level close to the lower limit of this range and the high dose (65 IU/kg) to achieve a peak activity level under the upper limit, taking into account an anticipated IR of 2 IU/dL per IU/kg, as described above. Four-week, repeated-dose toxicity studies of BIVV001 in rats and monkeys revealed a NOAEL of 750 IU/kg (Section 4.3.1), which is a dose level that is 30 times (30×) higher than the low dose for this study, and approximately 11.5× higher than the high dose.

As this is the first study of BIVV001 in humans, a step-wise dosing and data review/monitoring procedure (described in Section 7.1) will be followed in both the low-dose and high-dose cohorts to minimize the potential of adverse reactions occurring in several subjects. Additionally, following completion of dosing and data collection for the low-dose cohort, the Sponsor and an independent Data Safety Monitoring Committee (DSMC) will review all available data to determine the appropriateness of escalation to the higher BIVV001 dose; refer to Section 7.1 and Figure 1 for details.

5. SCHEDULES OF ACTIVITIES

Table 1: Screening Schedule (Both BIVV001 Low-Dose and High-Dose Cohorts)

Tests and Assessments[1]	Screening Visit (Visit 1)[2] Day -28 to Day 1	Repeat Screening Visit if >56 Days Elapse Prior to Advate Dosing[3]
Informed Consent[4]	X	
Assessment of Subject Eligibility[5]	X	X
Demographics[6]	X	
Medical, Surgical, and Hemophilia History[7]	X	X
CD4 Count, Viral Load (if known HIV^{+})[8]	X	X
HIV, HBV, and HCV Status[9]	X	X
Genotype, including [redacted][10] (Optional)	X	
Physical Examination (Including Height)	X	X
Vital Signs[11]	X	X
Weight	X	X
Hematology[12]	X	X
Clinical Chemistry[13]	X	X
Urinalysis[14]	X	X
Coagulation and Thrombosis Markers[15]	X	X
FVIII Activity (one-stage [aPTT-based] clotting and two-stage chromogenic assays)[16]	X	X

Tests and Assessments[1]	Screening Visit (Visit 1)[2] Day -28 to Day 1	Repeat Screening Visit if >56 Days Elapse Prior to Advate Dosing[3]
[redacted]	X	X
Nijmegen-Modified Bethesda Assay for Inhibitor[16]	X	X
Anti-rFVIIIFc-VWF-XTEN Antibody[16]	X	X
Serum and Plasma Samples[17] (Optional)	X	X
Adverse Event / Serious Adverse Event Reporting[18]	Ongoing: Monitor and record at all visits	
Concomitant Treatment/Procedure Recording[19]	Ongoing: Monitor and record at all visits	

BIV001 = rFVIIIFc-VWF-XTEN (recombinant coagulation factor VIII Fc - von Willebrand factor - XTEN fusion protein), BU = Bethesda units, FVIII = Factor VIII, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, [redacted]

1 Unscheduled visits may be necessary during the study to repeat any blood sampling if required.

2 Screening may be accomplished over the course of more than 1 study visit if needed. The Screening Period may be extended up to 120 days with prior Sponsor approval. If the Screening Period extends beyond 56 days, screening assessments must be repeated as specified in the Repeat Screening Visit column prior to dosing with Advate. Repeat laboratory assessments do not require site visit; samples may be collected via a home-nursing visit. Non laboratory assessments may be conducted on the same day as Advate dosing. See Table 6 for instructions for washout prior to the Advate dose. See Table 7 for instructions for treatment of bleeding, if applicable.

3 This visit need not be performed at the site. See Footnote 2 for details regarding Repeat Screening Visits.

4 Informed consent from the subject or the subject's legal guardian MUST be obtained prior to any study-related procedures, including washout of current therapy specifically for entry into the study. Subject assent must also be obtained where applicable (according to the study site's geographic region).

5 For Repeat Screening Visit, update with any changes since original Screening Visit.

6 Demographics include sex, race, ethnicity, and date of birth (year only), as permitted by local regulations. Race and ethnicity will be collected for reasons described in Section 17.4.

7 Includes assessment of disease severity, blood type, and Rh factor if not previously documented. For Repeat Screening Visit, update with any changes since original Screening Visit.

8 For subjects known to be HIV antibody positive, CD4 count and viral load tests must be performed at the central laboratory if results are not available from within 26 weeks prior to screening.

9 For subjects who have been historically negative, assess HIV, HBV, and HCV status with central laboratory test.

10 Collection of samples for genotype analysis (as permitted by local regulations and ethics committees) will be governed by a separate informed consent form (ICF). [redacted] Subjects may opt out of these assessments.

11 Vital signs include blood pressure, pulse rate, respiratory rate, and temperature (°C). Vital signs should be taken after the subject has been resting supine for 5 minutes. Vital signs should also be taken at any unscheduled visit.

[12] Hematology parameters include red blood cell (RBC) count, white blood cell (WBC) count and differential, platelet count, hemoglobin (Hgb), and hematocrit (Hct). Blood samples for hematology analysis will be collected prior to any FVIII dosing, including dosing with the most recent prior FVIII (prestudy FVIII).

[13] Clinical chemistry parameters include alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), bilirubin, blood urea nitrogen (BUN), creatinine, glucose, total protein, sodium, potassium, and chloride. Blood samples for clinical chemistry analysis will be collected prior to any FVIII dosing, including dosing with the most recent prior FVIII (prestudy FVIII).

[14] Urinalysis parameters include specific gravity, pH, color, appearance, leukocyte esterase, protein, glucose, ketones, occult blood, bilirubin, urobilinogen, nitrite, and microscopic examination of urine sediment. Urine samples for urinalysis will be collected prior to any FVIII dosing, including dosing with the most recent prior FVIII (prestudy FVIII).

[15] Coagulation and thrombosis markers include prothrombin time (PT), activated partial thromboplastin time (aPTT), D-dimer, international normalized ratio (INR), thrombin anti-thrombin (TAT) complex, prothrombin fragment 1.2, and the von Willebrand comprehensive panel (which includes assessments of von Willebrand Factor [VWF] ristocetin cofactor activity, and VWF antigen). Analysis of VWF multimers will be for future testing. Blood samples for analysis of coagulation and thrombosis markers will be collected prior to any FVIII dosing, including dosing with the most recent prior FVIII (prestudy FVIII).

[16] Trough sample only (collected prior to any prestudy FVIII dosing), to confirm severe hemophilia A (i.e., endogenous FVIII <1%) and to confirm that washout has occurred prior to inhibitor testing. This sample should be collected at the same time point as the inhibitor and anti-drug antibody (ADA) samples. Washout of at least 96 hours (for subjects on conventional FVIII product) and 120 hours (for subjects on EHL product) prior to sample collection is required. Separate samples for anti-rFVIIIFc-VWF-XTEN antibody (ADA) testing will be collected at the same time point when any samples are collected for inhibitor testing (including samples for suspected inhibitor and confirmatory inhibitor tests). Inhibitor and ADA samples will be collected prior to dosing on the day of any prestudy FVIII dosing.
All inhibitor assays, including the assay for the Screening Visit and any confirmatory assays, will be performed by the central laboratory using the Nijmegen-modified Bethesda assay. If a Nijmegen-modified Bethesda assay result returns as ≥0.6 BU/mL, a separate sample must be collected and tested for confirmation of inhibitor development within 2 to 4 weeks.
Testing for potential antibody formation will be performed at a central laboratory using a validated rFVIIIFc-VWF-XTEN-specific ADA assay. Confirmed positive samples will be further characterized for antibodies specific to Fc, FVIII, D′D3, or XTEN.

[17] Samples will be collected prior to any prestudy FVIII dosing and will be archived for testing by the central laboratory (if required) for future research, e.g., immunology assays, further coagulation assays, or clarification of any clinical or laboratory AE, etc. These tests will be governed by a separate ICF; subjects may opt out of these assessments.

[18] Adverse events and serious adverse events (SAEs) occurring after signing of ICF through the End of Study (EOS)/ Early Termination (ET) evaluations will be recorded on the case report form (CRF). Adverse events and SAEs should also be recorded at unscheduled visits.

[19] Concomitant medications and procedures from up to 30 days prior to screening through the EOS/ET evaluations will be recorded on the CRF.

Table 2: Advate Dosing and Pharmacokinetics Sampling Schedule (Both Low-Dose and High-Dose Cohorts)

Tests and Assessments[1]	Advate Dosing Visit (Visit 2; Day 1)[2]					Advate PK Visits (Visits 3 Through 5)		
	Visit 2					Visit 3	Visit 4	Visit 5
	Predose	Advate Dosing	30 min (±5 min)	1 h (±10 min)	6 h (±10 min)	24 h (±1 h)	48 h (±2 h)	72 h (±2 h)
Assessment of Subject Eligibility	X							
Vital Signs[3]	X	X	X	X	X	X	X	
Weight[4]	X							
Hematology[5]	X							
Clinical Chemistry[6]	X							
Urinalysis[7]	X							
Coagulation and Thrombosis Markers[8]	X			X	X	X		
FVIII Activity (one-stage clotting assay and chromogenic assay)	X[2]		X	X	X	X	X	X
[redacted]	X		X	X	X	X	X	X
Nijmegen-Modified Bethesda Assay for Inhibitor[9]	X							
Anti-rFVIIIFc-VWF-XTEN Antibody[9]	X							
Serum and Plasma Samples[10] (Optional)	X							
Advate Dosing (in clinic)		X						
Adverse Event / Serious Adverse Event Recording[11]	Ongoing: Monitor and record at all visits							
Concomitant Treatment/Procedure Recording[12]	Ongoing: Monitor and record at all visits							

BIV001 = rFVIIIFc-VWF-XTEN (recombinant coagulation factor VIII Fc - von Willebrand factor - XTEN fusion protein), BU = Bethesda units, FVIII = Factor VIII, PK = pharmacokinetics.

[1] Unscheduled visits may be necessary during the study to repeat any blood sampling if required.

[2] See Table 6 for instructions for washout prior to the Advate and BIVV001 doses. See Table 7 for instructions for treatment of bleeding, if applicable. PK sampling time points are measured relative to the start of injection. The predose sample should be taken within 30 minutes prior to the Advate injection.

[3] Vital signs include blood pressure, pulse rate, respiratory rate, and temperature (°C). Vital signs should be taken after the subject has been resting supine for 5 minutes. Vital signs should also be taken at any unscheduled visit.

[4] On the dosing day, weight will be used to calculate the Advate dose.

[5] Hematology parameters include RBC count, WBC count and differential, platelet count, Hgb, and Hct. Blood samples for hematology analysis will be collected prior to any FVIII dosing, including dosing with the most recent prior FVIII (prestudy FVIII).

[6] Clinical chemistry parameters include ALT, AST, ALP, GGT, bilirubin, BUN, creatinine, glucose, total protein, sodium, potassium, and chloride. Blood samples for clinical chemistry analysis will be collected prior to any FVIII dosing, including dosing with the most recent prior FVIII (prestudy FVIII).

[7] Urinalysis parameters include specific gravity, pH, color, appearance, leukocyte esterase, protein, glucose, ketones, occult blood, bilirubin, urobilinogen, nitrite, and microscopic examination of urine sediment. Urine samples for urinalysis will be collected prior to any FVIII dosing, including dosing with the most recent prior FVIII (prestudy FVIII).

[8] Coagulation and thrombosis markers include PT, aPTT, D-dimer, INR, TAT complex, prothrombin fragment 1.2, and the von Willebrand comprehensive panel (which includes assessments of von Willebrand Factor [VWF] ristocetin cofactor activity, and VWF antigen., Analysis of VWF multimers will be for future testing. Blood samples for analysis of coagulation and thrombosis markers will be collected prior to any FVIII dosing, including dosing with the most recent prior FVIII (prestudy FVIII).

[9] Washout of at least 96 hours for conventional products and at least 120 hours for EHL products prior to sample collection is required. Separate samples for anti-rFVIIIFc-VWF-XTEN antibody (anti-drug antibody; ADA) testing will be collected at the same time point when any samples are collected for inhibitor testing (including samples for suspected inhibitor and confirmatory inhibitor tests). Inhibitor and ADA samples will be collected prior to dosing on the day of Advate dosing.
All inhibitor assays, including the assay for the Screening Visit and any confirmatory assays, will be performed by the central laboratory using the Nijmegen-modified Bethesda assay. If a Nijmegen-modified Bethesda assay result returns as ≥0.6 BU/mL, a separate sample must be collected and tested for confirmation of inhibitor development within 2 to 4 weeks.
Testing for potential antibody formation will be performed at a central laboratory using a validated rFVIIIFc-VWF-XTEN-specific ADA assay. Confirmed positive samples will be further characterized for antibodies specific to Fc, FVIII, D′D3, or XTEN.

[10] Samples will be archived for testing by the central laboratory (if required) for future research, e.g., immunology assays, further coagulation assays, or clarification of any clinical or laboratory AE, etc. These tests will be governed by a separate ICF; subjects may opt out of these assessments.

[11] Adverse events and SAEs occurring after signing of the (ICF through the EOS/ET evaluations will be recorded on the CRF. Adverse events and SAEs should also be recorded at unscheduled visits.

[12] Concomitant medications and procedures from up to 30 days prior to screening through the EOS/ET evaluations will be recorded on the CRF.

Table 3: BIVV001 Dosing and Pharmacokinetics Sampling Schedule (BIVV001 Low-Dose Cohort Only)

	BIVV001 Dosing Visit[2] (After Advate Dosing Visit)								BIVV001 PK Visits (Visits 7 Through 13a) and 14-Day Inhibitor Test Visit (Visit 14)[1]							
	Visit 6[4]								Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13a	14-Day Inhibitor Test Visit[3] Visit 14
Tests and Assessments[1]	**Pre-dose**	**BIVV001 Dosing**	**10 min (±2 min)**	**30 min (±5 min)**	**1 h (±10 min)**	**3 h (±10 min)**	**6 h (±10 min)**	**9 h (±10 min)**	**24 h (±1 h)**	**48 h (±2 h)**	**72 h (±2 h)**	**96 h (±2 h)**	**120 h (±2 h)**	**168 h (±2 h)**	**240 h (±2 h)**	**336 h (±24 h for low-dose cohort)**
Vital Signs[5]	X	X	X	X	X	X	X	X	X	X						
Weight[6]	X															X
Hematology[7]	X															X
Clinical Chemistry[8]	X															X
Urinalysis[9]	X															X
Coagulation and Thrombosis Markers[10]	X				X		X		X							X
FVIII Activity (one-stage clotting assay and chromogenic assays)	X[2]		X	X	X	X	X	X	X	X	X	X	X	X	X	
[redacted]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Nijmegen-Modified Bethesda Assay for Inhibitor[11]	X															X

Tests and Assessments[1]	BIVV001 Dosing Visit[2] (After Advate Dosing Visit)								BIVV001 PK Visits (Visits 7 Through 13a) and 14-Day Inhibitor Test Visit (Visit 14)[1]							
	Visit 6[4]								Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13a	14-Day Inhibitor Test Visit[3] Visit 14
	Pre-dose	BIVV001 Dosing	10 min (±2 min)	30 min (±5 min)	1 h (±10 min)	3 h (±10 min)	6 h (±10 min)	9 h (±10 min)	24 h (±1 h)	48 h (±2 h)	72 h (±2 h)	96 h (±2 h)	120 h (±2 h)	168 h (±2 h)	240 h (±2 h)	336 h (±24 h for low-dose cohort)
Anti-rFVIIIFc-VWF-XTEN Antibody[11]	X															X
Serum and Plasma Samples[12] (Optional)	X															X
BIVV001 Dosing (in clinic)		X														
Adverse Event / Serious Adverse Event Recording[13]	Ongoing: Monitor and record at all visits															
Concomitant Treatment/ Procedure Recording[14]	Ongoing: Monitor and record at all visits															

BIV001 = rFVIIIFc-VWF-XTEN (recombinant coagulation factor VIII Fc – von Willebrand factor – XTEN fusion protein), BU = Bethesda units, FVIII = Factor VIII.

1 Unscheduled visits may be necessary during the study for safety and/or to repeat any blood sampling if required.

2 See Table 6 for instructions for washout prior to the BIVV001 dose. See Table 7 for instructions for treatment of bleeding, if applicable. PK sampling time points are measured relative to the start of injection. The predose sample should be taken within 30 minutes prior to the BIVV001 injection.

3 Subjects may resume treatment with their prestudy FVIII after completion of Visit 14 activities.

4 Visit 6 may be combined with Visit 5 for subjects in the low-dose cohort. If Visits 5 and 6 are combined, Visit 5 assessments may be performed at Visit 6.

[5] Vital signs include blood pressure, pulse rate, respiratory rate, and temperature (°C). Vital signs should be taken after the subject has been resting supine for 5 minutes. Vital signs should also be taken at any unscheduled visit.

[6] On the dosing day, weight will be used to calculate the BIVV001 dose.

[7] Hematology parameters include RBC count, WBC count and differential, platelet count, Hgb, and Hct. Blood samples for hematology analysis will be collected prior to any FVIII dosing, including dosing with the most recent prior FVIII (prestudy FVIII).

[8] Clinical chemistry parameters include ALT, AST, ALP, GGT, bilirubin, BUN, creatinine, glucose, total protein, sodium, potassium, and chloride. Blood samples for clinical chemistry analysis will be collected prior to any FVIII dosing, including dosing with the most recent prior FVIII (prestudy FVIII).

[9] Urinalysis parameters include specific gravity, pH, color, appearance, leukocyte esterase, protein, glucose, ketones, occult blood, bilirubin, urobilinogen, nitrite, and microscopic examination of urine sediment. Urine samples for urinalysis will be collected prior to any FVIII dosing, including dosing with the most recent prior FVIII (prestudy FVIII).

[10] Coagulation and thrombosis markers include PT, aPTT, D-dimer, INR, TAT complex, prothrombin fragment 1.2, and the von Willebrand comprehensive panel (which includes assessments of VWF ristocetin cofactor activity, and VWF antigen. Analysis of VWF multimers will be for future testing. Blood samples for analysis of coagulation and thrombosis markers will be collected prior to any FVIII dosing, including dosing with the most recent prior FVIII (prestudy FVIII).

[11] Washout of at least 3 days (72 hours) prior to sample collection is required. See Table 7 for instructions for treatment of bleeding. Separate samples for anti-rFVIIIFc-VWF-XTEN antibody (anti-drug antibody; ADA) testing will be collected at the same time point when any samples are collected for inhibitor testing (including samples for suspected inhibitor and confirmatory inhibitor tests). Inhibitor and ADA samples will be collected prior to dosing on the day of BIVV001 dosing.
All inhibitor assays, including the assay for the Screening Visit and any confirmatory assays, will be performed by the central laboratory using the Nijmegen-modified Bethesda assay. If a Nijmegen-modified Bethesda assay result returns as ≥0.6 BU/mL, a separate sample must be collected and tested for confirmation of inhibitor development within 2 to 4 weeks.
Testing for potential antibody formation will be performed at a central laboratory using a validated rFVIIIFc-VWF-XTEN-specific ADA assay. Confirmed positive samples will be further characterized for antibodies specific to Fc, FVIII, D′D3, or XTEN.

[12] Samples will be archived for testing by the central laboratory (if required) for future research, e.g., immunology assays, further coagulation assays, clarification of any clinical or laboratory AE, etc. These tests will be governed by a separate ICF; subjects may opt out of these assessments.

[13] Adverse events and SAEs occurring after signing of ICF through the EOS/ET evaluations will be recorded on the CRF. Adverse events and SAEs should also be recorded at unscheduled visits.

[14] Concomitant medications and procedures from up to 30 days prior to screening through the EOS/ET evaluations will be recorded on the CRF.

Table 4: BIVV001 Dosing and Pharmacokinetics Sampling Schedule (BIVV001 High-Dose Cohort Only)

	BIVV001 Dosing Visit[2] (After Advate Dosing Visit)								BIVV001 PK Visits (Visits 7 Through 13b) and 14-Day Inhibitor Test Visit (Visit 14)[1]								
	Visit 6								Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13a	Visit 13b	14-Day Inhibitor Test Visit[3] Visit 14
Tests and Assessments[1]	**Pre-dose**	**BIVV001 Dosing**	**10 min (±2 min)**	**30 min (±5 min)**	**1 h (±10 min)**	**3 h (±10 min)**	**6 h (±10 min)**	**9 h (±10 min)**	**24 h (±1 h)**	**48 h (±2 h)**	**72 h (±2 h)**	**96 h (±2 h)**	**120 h (±2 h)**	**168 h (±2 h)**	**240 h (±2 h)**	**288 h (±2 h)**	**336 h (±24 h for high-dose cohort)**
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X							
Weight[5]	X																X
Hematology[6]	X																X
Clinical Chemistry[7]	X																X
Urinalysis[8]	X																X
Coagulation and Thrombosis Markers[9]	X				X		X		X								X
FVIII Activity (one-stage clotting assay and chromogenic assay)	X[2]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Tests and Assessments[1]	BIVV001 Dosing Visit[2] (After Advate Dosing Visit)								BIVV001 PK Visits (Visits 7 Through 13b) and 14-Day Inhibitor Test Visit (Visit 14)[1]								
	Visit 6								Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13a	Visit 13b	14-Day Inhibitor Test Visit[3] Visit 14
	Pre-dose	BIVV001 Dosing	10 min (±2 min)	30 min (±5 min)	1 h (±10 min)	3 h (±10 min)	6 h (±10 min)	9 h (±10 min)	24 h (±1 h)	48 h (±2 h)	72 h (±2 h)	96 h (±2 h)	120 h (±2 h)	168 h (±2 h)	240 h (±2 h)	288 h (±2 h)	336 h (±24 h for high-dose cohort)
[redacted]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Nijmegen-Modified Bethesda Assay for Inhibitor[10]	X																X
Anti-rFVIIIFc-VWF-XTEN Antibody[10]	X																X
Serum and Plasma Samples[11] (Optional)	X																X
BIVV001 Dosing (in clinic)		X															
Adverse Event / Serious Adverse Event Recording[12]	Ongoing: Monitor and record at all visits																
Concomitant Treatment/ Procedure Recording[13]	Ongoing: Monitor and record at all visits																

BIV001 = rFVIIIFc-VWF-XTEN (recombinant coagulation factor VIII Fc - von Willebrand factor - XTEN fusion protein), BU = Bethesda units, FVIII = Factor VIII, PK = pharmacokinetics.

[1] Unscheduled visits may be necessary during the study to repeat any blood sampling if required.

[2] See Table 6 for instructions for washout prior to the BIVV001 dose. See Table 7 for instructions for treatment of bleeding, if applicable. PK sampling time points are measured relative to the start of injection. The predose sample should be taken within 30 minutes prior to the BIVV001 injection.

[3] For the high-dose cohort, the 14-day Inhibitor Test Visit will coincide with the 336 hour (14 day) visit for BIVV001 PK sampling at Visit 14. Subjects may resume treatment with their prestudy FVIII after completion of Visit 14 activities.

[4] Vital signs include blood pressure, pulse rate, respiratory rate, and temperature (°C). Vital signs should be taken after the subject has been resting supine for 5 minutes. Vital signs should also be taken at any unscheduled visit.

[5] On the dosing day, weight will be used to calculate the BIVV001 dose.

[6] Hematology parameters include RBC count, WBC count and differential, platelet count, Hgb, and Hct. Blood samples for hematology analysis will be collected prior to any FVIII dosing, including dosing with the most recent prior FVIII (prestudy FVIII).

[7] Clinical chemistry parameters include ALT, AST, ALP, GGT, bilirubin, BUN, creatinine, glucose, total protein, sodium, potassium, and chloride. Blood samples for clinical chemistry analysis will be collected prior to any FVIII dosing, including dosing with the most recent prior FVIII (prestudy FVIII).

[8] Urinalysis parameters include specific gravity, pH, color, appearance, leukocyte esterase, protein, glucose, ketones, occult blood, bilirubin, urobilinogen, nitrite, and microscopic examination of urine sediment. Urine samples for urinalysis will be collected prior to any FVIII dosing, including dosing with the most recent prior FVIII (prestudy FVIII).

[9] Coagulation and thrombosis markers include PT, aPTT, D-dimer, INR, TAT complex, prothrombin fragment 1.2, and the von Willebrand comprehensive panel (which includes assessments of VWF ristocetin cofactor activity, and VWF antigen). Analysis of VWF multimers will be for future testing. Blood samples for analysis of coagulation and thrombosis markers will be collected prior to any FVIII dosing, including dosing with the most recent prior FVIII (prestudy FVIII).

[10] Washout of at least 4 days (96 hours) prior to sample collection is required. See Table 7 for instructions for treatment of bleeding. Separate samples for anti-rFVIIIFc-VWF-XTEN antibody (anti-drug antibody; ADA) testing will be collected at the same time point when any samples are collected for inhibitor testing (including samples for suspected inhibitor and confirmatory inhibitor tests). Inhibitor and ADA samples will be collected prior to dosing on the day of BIVV001 dosing.
All inhibitor assays, including the assay for the Screening Visit and any confirmatory assays, will be performed by the central laboratory using the Nijmegen-modified Bethesda assay. If a Nijmegen-modified Bethesda assay result returns as ≥0.6 BU/mL, a separate sample must be collected and tested for confirmation of inhibitor development within 2 to 4 weeks.
Testing for potential antibody formation will be performed at a central laboratory using a validated rFVIIIFc-VWF-XTEN-specific ADA assay. Confirmed positive samples will be further characterized for antibodies specific to Fc, FVIII, D′D3, or XTEN.

[11] Samples will be archived for testing by the central laboratory (if required) for future research, e.g., immunology assays, further coagulation assays, clarification of any clinical or laboratory AE, etc. These tests will be governed by a separate ICF; subjects may opt out of these assessments.

[12] Adverse events and SAEs occurring after signing of the ICF through the EOS/ET evaluations will be recorded on the CRF. Adverse events and SAEs should also be recorded at unscheduled visits.

[13] Concomitant medications and procedures from up to 30 days prior to screening through the EOS/ET evaluations will be recorded on the CRF.

Table 5: End-of-Study / Early Termination Evaluation Schedule for Advate and BIVV001 (Both Low-Dose and High Dose Cohorts)

Tests and Assessments [1]	End of Study/Early Termination [2]	
	Visit 15 [3]	Post-Advate Follow-Up Safety Telephone Call [4]
	28 days (±5 days) after BIVV001 dose	
Physical Examination	X	
Vital Signs[5]	X	
Weight	X	
Hematology[6]	X	
Clinical Chemistry[7]	X	
Urinalysis[8]	X	
Coagulation and Thrombosis Markers[9]	X	
FVIII Activity (one-stage clotting assay and chromogenic assay)	X	
[redacted]	X	
Nijmegen-Modified Bethesda Assay for Inhibitor[10]	X	
Anti-rFVIIIFc-VWF-XTEN Antibody[10]	X	
Serum and Plasma Samples[11] (Optional)	X	
Follow-Up Safety Telephone Call		X
Adverse Event / Serious Adverse Event Recording[12]	Ongoing: Monitor and record at all visits	
Concomitant Treatment/Procedure Recording[13]	Ongoing: Monitor and record at all visits	

BIV001 = rFVIIIFc-VWF-XTEN (recombinant coagulation factor VIII Fc – von Willebrand factor – XTEN fusion protein), BU = Bethesda units, FVIII = Factor VIII, PK = pharmacokinetics.

[1] Unscheduled visits may be necessary during the study to repeat any blood sampling if required.

[2] If a subject is withdrawn from the study early, the Investigator will make every effort to complete and report the reason(s) for withdrawal as thoroughly as possible on the subject's CRF. Subjects who withdraw from the study may be replaced; refer to Section 10.1.3.

[3] The activities listed in this column will be performed for the following subjects: those who were administered BIVV001 *and* successfully completed the 28-day safety observation period; those who were administered BIVV001 *but were withdrawn from the study* (for any reason other than withdrawal of consent) prior to completing the 28-day safety observation period (refer to Section 10.1.2). Subjects who complete these activities (whether performed at the conclusion of the 28-day safety observation period or as an early-termination visit) are not required to participate in the post-Advate follow-up safety telephone call.

[4] The post-Advate follow-up safety telephone call is required for subjects who were withdrawn from the study (for any reason other than withdrawal of consent) *prior to* BIVV001 administration (refer to Section 10.1.1 for withdrawal criteria). The telephone call must be completed between 7 to 14 days from the time of Advate administration, or as soon as possible thereafter.

[5] Vital signs include blood pressure, pulse rate, respiratory rate, and temperature (°C). Vital signs should be taken after the subject has been resting supine for 5 minutes. Vital signs should also be taken at any unscheduled visit.

[6] Hematology parameters include RBC count, WBC count and differential, platelet count, Hgb, and Hct. Blood samples for hematology analysis will be collected prior to any FVIII dosing, including dosing with the most recent prior FVIII (prestudy FVIII).

[7] Clinical chemistry parameters include ALT, AST, ALP, GGT, bilirubin, BUN, creatinine, glucose, total protein, sodium, potassium, and chloride. Blood samples for clinical chemistry analysis will be collected prior to any FVIII dosing, including dosing with the most recent prior FVIII (prestudy FVIII).

[8] Urinalysis parameters include specific gravity, pH, color, appearance, leukocyte esterase, protein, glucose, ketones, occult blood, bilirubin, urobilinogen, nitrite, and microscopic examination of urine sediment. Urine samples for urinalysis will be collected prior to any FVIII dosing, including dosing with the most recent prior FVIII (prestudy FVIII).

[9] Coagulation and thrombosis markers include PT, aPTT, D-dimer, INR, TAT complex, prothrombin fragment 1.2, and the von Willebrand comprehensive panel (which includes assessments of VWF ristocetin cofactor activity, and VWF antigen. Analysis of VWF multimers will be for future testing. Blood samples for analysis of coagulation and thrombosis markers will be collected prior to any FVIII dosing, including dosing with the most recent prior FVIII (prestudy FVIII).

[10] Washout of at least 48 hours prior to the inhibitor test is required. Separate samples for anti-rFVIIIFc-VWF-XTEN antibody (anti-drug antibody; ADA) testing will be collected at the same time point when any samples are collected for inhibitor testing (including samples for suspected inhibitor and confirmatory inhibitor tests). Inhibitor and ADA samples will be collected prior to dosing on the day of any prestudy FVIII dosing.
All inhibitor assays, including the assay for the Screening Visit and any confirmatory assays, will be performed by the central laboratory using the Nijmegen-modified Bethesda assay. If a Nijmegen-modified Bethesda assay result returns as ≥0.6 BU/mL, a separate sample must be collected and tested for confirmation of inhibitor development within 2 to 4 weeks.
Testing for potential antibody formation will be performed at a central laboratory using a validated rFVIIIFc-VWF-XTEN-specific ADA assay. Confirmed positive samples will be further characterized for antibodies specific to Fc, FVIII, D′D3, or XTEN.

[11] Samples will be archived for testing by the central laboratory (if required) for future research, e.g., immunology assays, further coagulation assays, clarification of any clinical or laboratory AE, etc. These tests will be governed by a separate ICF; subjects may opt out of these assessments.

[12] Adverse events and SAEs occurring after signing of the ICF through the EOS/ET evaluations will be recorded on the CRF. Adverse events and SAEs should also be recorded at unscheduled visits.

[13] Concomitant medications and procedures from up to 30 days prior to screening through the EOS/ET evaluations will be recorded on the CRF.

Table 6: Instructions for Washout, Dosing, and Pharmacokinetic Sampling

The following steps are to be followed if no bleeding episode occurs:

Screening

Subjects may continue prophylaxis with their most recent previous FVIII product (referred to as prestudy FVIII), except during the following activities:

- The washout prior to Screening test of FVIII activity and inhibitor tests and prior to Advate dose administration: this washout duration must be at least 96 hours (4 days) if the prestudy FVIII is a conventional product; it must be at least 120 hours (5 days) if the prestudy FVIII is an EHL product.

Advate PK sampling

- PK sampling duration is 72 hours (3 days) for both the low-dose and high-dose cohort.

Washout prior to BIVV001 dose

- Washout duration is at least 72 hours (3 days) after a low dose of Advate; the duration is at least 96 hours (4 days) after a high dose of Advate. This washout duration may overlap with the Advate PK sampling period.

BIVV001 dose and PK sampling

- The BIVV001 dose must be administered 3 (+1) days in the low-dose cohort after the Advate dose, and 4 (+1) days in the high-dose cohort after the Advate dose.
- PK sampling duration is 10 days for the low-dose cohort and 14 days for the high-dose cohort.

After completion of Visit 14 activities (which include the 14-day inhibitor test)

- Subjects may resume treatment with their prestudy FVIII therapy
- If the subject resumes prestudy FVIII during this time, a washout of at least 48 hours is required prior to sample collection for the End of Study (EOS)/Early Termination (ET) inhibitor test

BIV001 = rFVIIIFc-VWF-XTEN (recombinant coagulation factor VIII Fc - von Willebrand factor - XTEN fusion protein), FVIII = Factor VIII, PK = pharmacokinetics.

Table 7: Instructions for Treatment of Bleeding Episodes

Investigator must instruct the subject on the pre-study FVIII regimen for treatment of bleeding episodes. Please refer to the Study Reference Guide for details regarding the treatment of bleeding episodes during the study.

If the bleed occurs:	Take the following action(s):
During screening prior to the pre-Advate washout[1]	Treat the bleeding episode with prestudy FVIII Subsequent steps as described in Table 6
During washout prior to Advate dose [1]	Treat the bleeding episode with prestudy FVIII If 1 bleeding episode occurs during this period: • Repeat washout prior to Advate: – Washout duration may be modified to at least 96 hours (4 days) if the prestudy FVIII is a conventional product; washout duration is at least 120 hours (5 days) if EHL product • Subsequent steps as described in Table 6 If more than 1 bleeding episode occurs during this period: discontinue the subject from further study participation.[2] As these events occurred prior to study enrollment, the subject will be designated a screen failure.
During the PK sampling period for Advate	Treat the bleeding episode with prestudy FVIII If 1 bleeding episode occurs during this period: • Repeat washout prior to Advate: – Washout duration may be modified to at least 96 hours (4 days) if the prestudy FVIII is a conventional product; washout duration is at least 120 hours (5 days) if EHL product • Repeat Advate dose and PK sampling • Subsequent steps as described in Table 6 If more than 1 bleeding episode occurs or more than 28 days elapse as a result of a bleeding episode between the Advate dose and the planned BIVV001 dose: discontinue further study treatment and end further PK sampling.[2] The subject must participate in a post-Advate follow-up safety telephone call (Table 5; Section 10.1.1) to be officially withdrawn from the study.

If the bleed occurs:	Take the following action(s):
During the washout prior to BIVV001 dose and after completion of Advate PK sampling (if applicable)	Treat the bleeding episode with prestudy FVIII If no more than 28 days elapse between the Advate dose and the planned BIVV001 dose: • Repeat washout prior to BIVV001 – Washout duration is at least 96 hours (4 days) after the FVIII dose for a conventional product or at least 120 hours (5 days) if EHL product • Subsequent steps as described in Table 6 If more than 1 bleeding episode occurs or 28 days elapse as a result of a bleeding event between the Advate dose and the planned BIVV001 dose: discontinue further study treatment and end further PK sampling.[2] The subject must participate in a post-Advate follow-up safety telephone call (Table 5; Section 10.1.1) to be officially withdrawn from the study.
During the PK sampling period for BIVV001	Treat the bleeding episode with prestudy FVIII. End further PK sampling. The subject will remain in the study to complete the remaining inhibitor and other safety assessments of the 28-day safety observation period and the EOS/ET evaluations (Table 5).[2]
During follow-up after completion of Visit 14 activities	After completion of Visit 14 activities (which includes the 14-day inhibitor test), subjects may resume treatment with their prestudy FVIII. • Treat the bleeding episode with prestudy FVIII • If a subject experiences two or more spontaneous bleeds between Day 14 and Day 28, the investigator will notify the sponsor. • If the subject resumes prestudy FVIII during this time, a washout of at least 48 hours is required prior to sample collection for the EOS/ET inhibitor test.

BIV001 = rFVIIIFc-VWF-XTEN (recombinant coagulation factor VIII Fc - von Willebrand factor - XTEN fusion protein), FVIII = Factor VIII, PK = pharmacokinetics.

[1] The Screening Period (including the washout prior to Advate) may be extended up to 120 days with prior Sponsor approval. If the Screening Period extends beyond 56 days, screening assessments must be repeated as specified in Table 1 prior to dosing with Advate. Repeat laboratory assessments do not require site visit; samples may be collected via a home-nursing visit. Non-laboratory assessments may be conducted on the same day as Advate dosing.

[2] Replace the subject if needed to ensure that at least 6 subjects from the low-dose cohort and at least 8 subjects from the high-dose cohort provide evaluable PK and inhibitor data.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoints

The primary objective is to assess the safety and tolerability of a single IV administration of BIVV001 in adult previously treated patients (PTPs) with severe hemophilia A.

The primary endpoints are as follows:

- The occurrence of adverse events (AEs)
- The occurrence of clinically significant abnormalities in laboratory tests, including development of inhibitors (neutralizing antibodies directed against FVIII) as determined by the Nijmegen-modified Bethesda assay.

6.2. Secondary Objective and Endpoints

The secondary objective is to characterize the PK of BIVV001 after a single IV administration compared with the PK of Advate, with FVIII activity determined by the one-stage (activated partial thromboplastin time [aPTT]-based) clotting assay.

The secondary endpoints are PK parameters, including but not limited to the following: maximum activity (C_{max}); $t_{½}$; CL; volume of distribution at steady state (V_{ss}); area under the concentration-time curve from time 0 to infinity (AUC_{∞}); mean residence time (MRT); IR; and time to 1% above baseline for FVIII activity.

6.3. Exploratory Objective and Endpoints

The exploratory objective is to characterize the PK of BIVV001 after a single IV administration compared with the PK of Advate, with FVIII activity determined by the two-stage chromogenic assay.

The exploratory endpoints are PK parameters, including but not limited to the following: C_{max}, $t_{½}$, CL, V_{ss}, AUC_{∞}, MRT, IR, and time to 1% above baseline for FVIII activity.

7. STUDY DESIGN

7.1. Study Overview

This is a Phase 1/2a, open-label, dose-escalation, multicenter study designed to evaluate the safety, tolerability, and PK of a single IV dose of BIVV001 in subjects with severe hemophilia A who have received at least 150 exposure days (EDs) of prior FVIII treatment.

Approximately 18 male PTPs aged 18 to 65 years will be enrolled: approximately 8 subjects in the low-dose cohort (Advate 25 IU/kg and BIVV001 25 IU/kg) and approximately 10 subjects in the high-dose cohort (Advate 65 IU/kg and BIVV001 65 IU/kg). Each subject will be dosed with Advate followed by a PK sampling period. Following a brief washout period, each subject will then be administered BIVV001 followed by a PK sampling period. Subjects will undergo safety observation for 28 days following the injection of BIVV001, including sample collection for inhibitor assessments 14 and 28 days after the injection of BIVV001 (refer to Figure 1 and Sections 11.1.1 and 11.1.2 for details on treatment and sample collection regimens). Only subjects who are able to provide adequate samples for PK and inhibitor characterization following both Advate and BIVV001 dosing will be considered to be evaluable; additional subjects will be enrolled as needed to ensure that at least 6 subjects in the low-dose cohort and 8 subjects in the high-dose cohort provide evaluable PK and inhibitor data.

To minimize the potential of adverse reactions occurring in several subjects, the following step-wise procedures will be utilized to administer BIVV001:

1. For the low-dose cohort, data collected for inhibitor test results and other available safety assessments through 28 days post-BIVV001 dose for Subject 1 must be reviewed before permitting administration of BIVV001 to Subject 2, and the same data through 28 days post-BIVV001 dose must be reviewed before permitting administration of BIVV001 to Subject 3. After BIVV001 administration to Subject 3, data will be reviewed for inhibitor test results and other available safety assessments through 14 days post-BIVV001 dose, before permitting administration of BIVV001 to Subject 4 [Abbas 2007]. For Subjects 4 through 8 of this cohort, an interval of at least 72 hours must elapse between BIVV001 dose administrations to successive subjects.

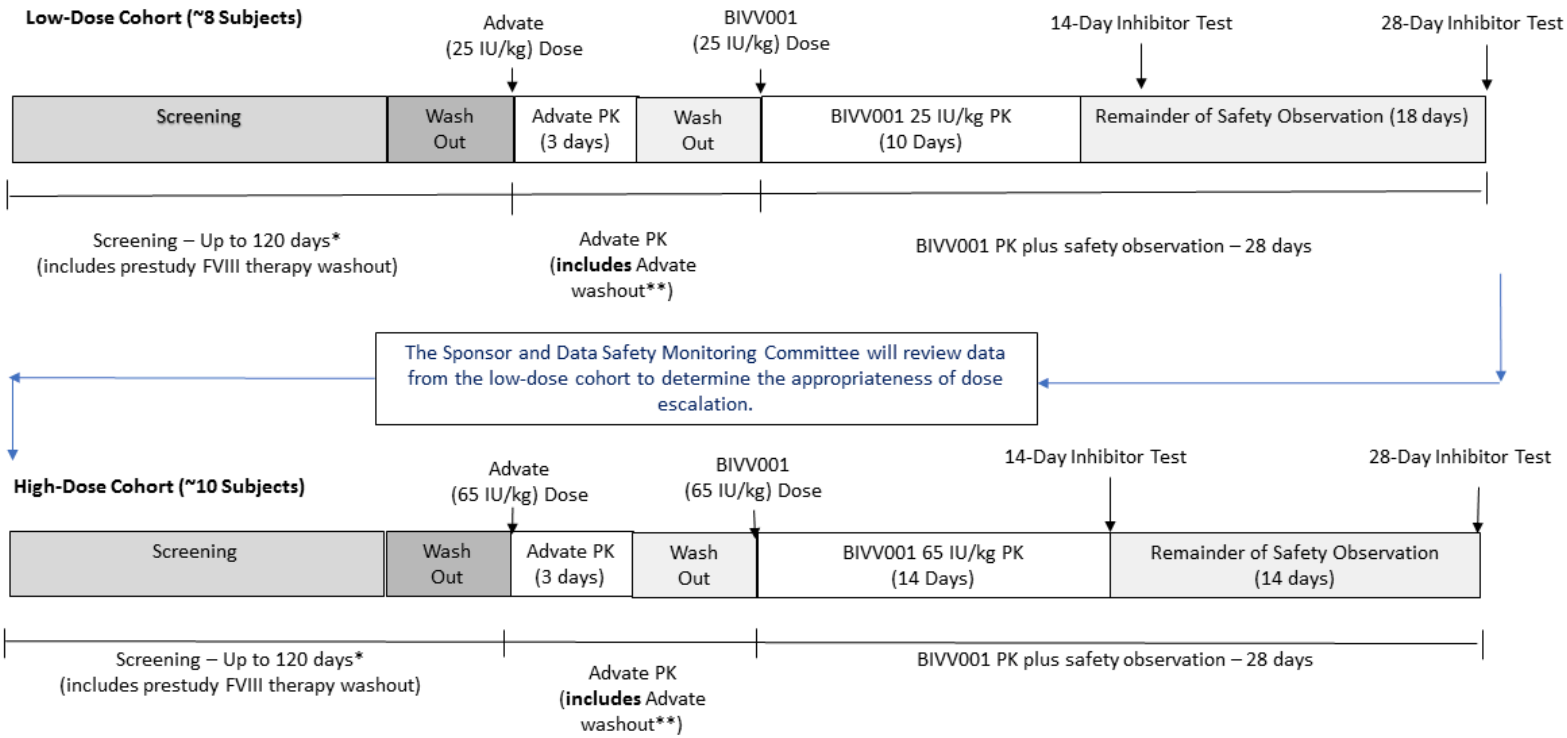
2. Before proceeding to the high-dose cohort, the Sponsor and the DSMC will review available data obtained from the low-dose cohort to determine whether it is appropriate to begin administration of the higher BIVV001 dose.

3. For the high-dose cohort, data collected for inhibitor test results and other available safety assessments through 28 days post-BIVV001 dose for Subject 1 must be reviewed before permitting administration of BIVV001 to Subject 2, and the same data through 28 days post-BIVV001 dose must be reviewed before permitting administration of BIVV001 to Subject 3. After BIVV001 administration to Subject 3, data will be reviewed for inhibitor test results and other available safety assessments through 14 days post-BIVV001 dose,

before permitting administration of BIVV001 to Subject 4 [Abbas 2007]. For Subjects 4 through 10 of this cohort, an interval of at least 96 hours must elapse between BIVV001 administrations to successive subjects.

Refer to Figure 1 for a schematic of the study design.

Figure 1: Study Design



* Screening may be extended up to 120 days with prior Sponsor approval. If the Screening Period extends beyond 56 days, screening assessments must be repeated as specified in Table 1 prior to dosing with Advate. Washout duration at least 96 hours (4 days) from the most recent FVIII dose (prestudy FVIII) for a conventional product, 120 hours (5 days) for an extended half-life FVIII product.

** Washout duration at least 72 hours (3 days) from the Advate dose for the BIVV001 low-dose cohort, and at least 96 hours (4 days) for the BIVV001 high-dose cohort.

7.1.1. Dose-Limiting Toxicity

Each subject in this study will receive a single IV dose of Advate (either 25 IU/kg or 65 IU/kg) and a single IV dose of BIVV001 (either 25 IU/kg or 65 IU/kg). Investigators will not be asked to determine dose-limiting toxicities (DLTs) in this study. Certain postdose events may result in a meeting between the Sponsor and DSMC to determine the appropriateness of dosing subsequent subjects. For details, refer to Section 7.6.1 (dose suspension) and Section 7.6.2 (dose termination).

7.2. Overall Study Duration and Follow-Up

The study will consist of 3 periods: a 28-day screening period (extendable to 120 days; refer to Section 7.2.1); an Advate dosing and PK sampling period (which also includes an Advate washout that may overlap with PK sampling); a BIVV001 dosing and PK sampling period, and a 28-day safety observation period (in which PK sampling and safety observation will overlap during the first 10 to 14 days of this period).

It is anticipated that subjects in the low-dose cohort will visit the study clinic approximately 4 to 15 times, depending on how many home nursing visits occur: 4 of these visits will include medical evaluation and sample collection, while the other 11 visits will include sample collection only (refer to Table 2 and Table 3). For subjects in the high-dose cohort, it is anticipated that they will visit the clinic approximately 4 to 16 times, depending on how many home nursing visits occur: 4 of these visits will include medical evaluation and sample collection, while the other 12 visits will include sample collection only (refer to Table 2 and Table 4).

7.2.1. Screening Period (Including Initial Wash Out)

The Screening Period for determination of subject eligibility is scheduled within 28 days prior to the dose of Advate (and may be extended up to 120 days with prior Sponsor approval); refer to Table 1. If the Screening Period extends beyond 56 days, screening assessments must be repeated as specified in Table 1 prior to dosing with Advate. The Screening Period includes washout of the subject's prior FVIII treatment (hereinafter referred to as the prestudy FVIII) prior to screening assessments and prior to the Advate dosing and PK sampling period. Prestudy FVIII washout duration is at least 96 hours (4 days) from the most recent prestudy FVIII dose for subjects who received a conventional FVIII product and at least 120 hours (5 days) for subjects who received an EHL FVIII product (rFVIIIFc or other products). Washout procedures for conventional FVIII products may be modified if the subject experiences a bleeding episode. Refer to Table 6 for detailed washout instructions; refer to Table 7 for detailed instructions on the treatment of bleeding episodes. Subjects who do not meet eligibility requirements at screening will not be allowed to repeat screening at a later date.

7.2.2. Low-Dose Cohort

In the low-dose cohort, Advate and BIVV001 dosing will begin at 25 IU/kg. All doses of Advate and BIVV001 will be administered IV by the Investigator or his/her designee under medical

supervision, with an injection duration of 8 ± 2 minutes. Details describing the treatment and sample collection regimen for the low-dose cohort are provided in Section 11.1.1.

The following are the key elements of the low-dose cohort:

- After completing the Screening Period, subjects will receive a single IV dose of Advate followed by a 72-hour (3-day) PK sampling period; see Table 2.
- Prophylactic dosing with prestudy FVIII therapy is not permitted between Advate and BIVV001 dosing.
- After washout of Advate, subjects will receive a single open-label IV dose of 25 IU/kg BIVV001 followed by a 240-hour (10-day) sampling period (see Table 3).
- To minimize the potential of adverse reactions occurring in several subjects, a step-wise dosing and data review/monitoring procedure will be followed between BIVV001 administrations to successive subjects in the low-dose cohort.
- BIVV001 25 IU/kg must be administered 3 (+1) days following administration of 25 IU/kg Advate.
- If the dose of BIVV001 cannot be administered per these guidelines, the administration of BIVV001 may occur within a window of up to 4 additional days at the discretion of the Investigator, i.e., up to 7 days following 25 IU/kg Advate.
- The Investigator must notify the sponsor and provide rationale if the dose of BIVV001 is administered beyond 96 hours (4 days) following Advate administration.
- If a bleeding event is detected between Advate dosing and BIVV001 dosing, no more than 28 days may elapse between Advate and BIVV001 dosing (refer to the instructions in Table 7).

7.2.3. Escalation to High-Dose Cohort

Upon availability of data from the low-dose cohort, the Sponsor and the DSMC will review the data and decide on the appropriateness of escalation to the high dose (65 IU/kg) as detailed in the DSMC charter. If the Sponsor and DSMC determine that dose escalation can proceed, additional new subjects will be enrolled in the high-dose cohort.

7.2.4. High-Dose Cohort

In the high-dose cohort, Advate and BIVV001 dosing will begin at 65 IU/kg. All doses of Advate and BIVV001 will be administered IV by the Investigator or his/her designee under medical supervision, with an injection duration of 8 ± 2 minutes. Details describing the treatment and sample collection regimen for the high-dose cohort are provided in Section 11.1.2.

The following are the key elements of the high-dose cohort:

- After completing the Screening Period, subjects will receive a single IV dose of Advate followed by a 72-hour (3-day) sampling period (see Table 2).
- Prophylactic dosing with prestudy FVIII therapy is not permitted between Advate and BIVV001 dosing.
- After washout of Advate, subjects will receive a single open-label IV dose of BIVV001 followed by a 336-hour (14-day) sampling period (see Table 4).
- As with the low-dose cohort, an identical, step-wise dosing and data review/monitoring procedure will be followed between BIVV001 administrations to successive subjects in the high-dose cohort (Section 7.1).
- BIVV001 65 IU/kg must be administered 4 (1) days following administration of 65 IU/kg Advate.
- If the dose of BIVV001 cannot be administered per these guidelines, the administration of BIVV001 may occur within a window of up to 4 days at the discretion of the Investigator, i.e. up to 8 days following 65 IU/kg Advate.
- The Investigator must notify the sponsor and provide rationale if the dose of BIVV001 is administered beyond 120 hours (5 days) following Advate administration.
- If a bleeding event is detected between Advate dosing and BIVV001 dosing, no more than 28 days may elapse between Advate and BIVV001 dosing (refer to the instructions in Table 7).

7.2.5. Safety Observation Period

The 28-day safety observation period starts on the day the subject receives the single IV dose of BIVV001 and overlaps with the PK sampling period for BIVV001.

Subjects may resume treatment with their prestudy FVIII product during the 28-day safety observation period after completing Visit 14 activities (which include the 14-day inhibitor test; refer to Table 3 and Table 4).

Final assessments for the study are performed in the End of Study (EOS)/Early Termination (ET) evaluations; see Table 5. Subjects who are withdrawn from the study (for reasons other than withdrawal of consent) prior to BIVV001 administration will be asked to participate in a post-Advate follow-up safety telephone call; see Table 5 and Section 10.1.1. Subjects who are administered BIVV001 and either complete the 28-day safety observation period or are withdrawn from the study (for reasons other than withdrawal of consent) prior to completion of the safety observation period (see Section 10.1.2) will be asked to submit

to Visit 15 procedures (Table 5). The post-Advate follow-up safety telephone call is not required for subjects who complete Visit 15 procedures.

7.3. Study Duration for Subjects

The total time on study for each subject is expected to range from approximately 60 to 156 days, depending on the length of Screening Period and the cohort to which the subject is assigned. Time on study is comprised of the following:

- Up to 28 days for screening and washout of prestudy FVIII therapy prior to Advate dosing (the screening period may be extended up to 120 days with prior Sponsor approval). If the Screening Period extends beyond 56 days, screening assessments must be repeated as specified in Table 1 prior to dosing with Advate.
- At least 3 days (low-dose cohort) or 4 days (high-dose cohort) of Advate PK sampling/washout following Advate dose administration
- 28 days of safety observation (which includes 10 to 14 days of BIVV001 PK sampling) following BIVV001 dose administration.

Further details are provided in the Section 5. Durations may vary for scheduling reasons or if a bleeding episode occurs; see Table 7 for further details regarding treatment of a bleeding episode.

The end-of-study date for a subject is the last study visit or the last follow-up telephone conversation.

7.4. Responsibilities of Study Site Personnel

Refer to Study Reference Guide.

7.5. Substudy Design

No substudies are planned for this study.

7.6. Study Stopping Rules

The Sponsor may terminate the study at any time, after informing Investigators, Institutional Review Boards/Ethics Committees (ECs), and applicable regulatory agencies. Investigators will be notified by the Sponsor (or designee) if enrollment and dosing are suspended, completed, or closed.

7.6.1. Dose and Enrollment Suspension

The occurrence of specific study events will require that further enrollment in the study and further dosing be suspended. In this situation, the event will be investigated prior to enrollment or dosing of any additional subjects.

The events requiring dose and enrollment suspension are as follows:

- Development of inhibitor (a result of ≥0.6 Bethesda units per mL [BU/mL] identified and confirmed by a second test on an independent sample collected within 2 weeks to 4 weeks of the first positive sample, with both tests performed by the central laboratory using the Nijmegen-modified Bethesda assay) following administration of BIVV001.

- A low VWF ristocetin cofactor (VWF:RCo < 30 IU/dL identified and confirmed by a second test on an independent sample collected 1 to 4 weeks after the first low result, with both tests performed by the central laboratory) following the administration of BIVV001.

- Two or more subjects experience serious adverse events (SAEs) that are assessed by the Investigator to be related to BIVV001

- The Investigator, Sponsor, Medical Monitor, and/or DSMC determine that an event or current data warrant further evaluation by the DSMC.

Actions to be taken for subjects already participating in the study at the time of dose and enrollment suspension will depend on whether the suspension occurred prior to or after the subject received BIVV001:

a. Subjects who have not yet received BIVV001 will suspend further study procedures (including BIVV001 administration); subjects who have received Advate will complete the procedures described for the Advate PK sampling period.
b. Subjects who have received BIVV001 will remain on the protocol schedule (to complete the BIVV001 PK sampling period, the 28-day safety observation period, and the EOS/ET evaluations), unless the DSMC, Investigator, Sponsor, or Medical Monitor advise otherwise (i.e., longer duration and/or additional follow-up is needed).

The DSMC will review the data concerning the event and subject, with input from the Investigator, along with all other available data. Based on the results of its investigation, the DSMC and/or Sponsor will determine appropriate follow-up and decide whether study enrollment and dosing should resume.

7.6.2. Dose and Enrollment Termination

The occurrence of specific study events will require that further enrollment in the study and further dosing be terminated. If study enrollment and dosing are terminated, the Investigators will be notified and the DSMC will review the available data.

The events requiring dose and enrollment termination are as follows:

- Unacceptable inhibitor frequency, including high-titer inhibitor frequency, as advised by the Sponsor and/or DSMC following administration of BIVV001

- Death at any time during the study that is assessed by the Investigator and/or Sponsor to be related to BIVV001

- The Investigator, Sponsor, Medical Monitor, and/or DSMC determine that an event or current data warrant termination of dosing and enrollment.

Actions to be taken for subjects already participating in the study at the time of dose and enrollment termination will depend on whether the termination occurred prior to or after the subject received BIVV001:

a. Subjects who have not yet received BIVV001 will stop further study procedures (including BIVV001 administration) and will be asked to perform the EOS/ET evaluations (including the post-Advate follow-up safety telephone call); see Table 5.
b. Subjects who have received BIVV001 will remain on the protocol schedule (to complete the BIVV001 PK sampling period, the 28-day safety observation period, and the EOS/ET evaluations; see Table 5), unless the DSMC, Investigator, Sponsor, or Medical Monitor advise otherwise (i.e., longer duration and/or additional follow up is needed).

Bioverativ will notify Investigators and IQVIA when the study is to be placed on hold, completed, or terminated.

7.7. End of Study

The EOS is the last visit or the last follow-up telephone call of the last subject.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at screening, or at the time point specified in the individual eligibility criterion listed:

1. Ability of the subject, or his legally authorized representative (e.g., parent or legal guardian) if applicable in accordance with local regulations, to understand the purpose and risks of the study and provide signed and dated informed consent/assent and authorization to use confidential health information in accordance with national and local subject privacy regulations.

2. Male, aged 18 to 65 years, inclusive, at the time of informed consent.

3. Severe hemophilia A, defined as <1 IU/dL (<1%) endogenous FVIII at screening as determined by the one-stage clotting assay from the central laboratory. If the initial screening result is ≥1%, then a repeat endogenous FVIII activity level will be performed using the using the one stage clotting assay from the central laboratory. If the repeated result is <1 IU/dL (<1%), then the subject will meet this inclusion requirement.

4. Previous treatment for hemophilia A, defined as at least 150 documented prior EDs to any recombinant and/or plasma-derived FVIII and/or cryoprecipitate products at Day 1. Fresh frozen plasma treatment must not be considered in the count for documented exposure days.

5. Platelet count ≥100,000 cells/μL at screening (test performed by the central laboratory and reviewed prior to the Day 1 Advate dose).

6. A subject known to be human immunodeficiency virus (HIV) antibody positive, either previously documented or identified from screening assessments, must have the following results prior to Day 1 Advate dose.

   a. CD4 lymphocyte count >200 cells/mm³

   b. Viral load of <400 copies/mL

   Documented results of CD4 lymphocyte count and viral load will be accepted if samples were collected within 26 weeks prior to screening or if samples were collected during screening and evaluated by the central laboratory.

   Subjects who have previously tested negative for HIV must have a repeat test by the central laboratory during Screening.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at screening, or at the time point specified in the individual criterion listed:

Medical History

1. Any concurrent clinically significant major disease that, in the opinion of the Investigator, would make the subject unsuitable for enrollment.

2. Serious active bacterial or viral infection (other than chronic hepatitis or HIV) present within 30 days of screening.

3. Other known coagulation disorder(s) in addition to hemophilia A.

4. History of hypersensitivity or anaphylaxis associated with any FVIII product.

5. Known or suspected allergy to mice, hamsters, or any ingredient in Advate

6. History of a positive inhibitor test or clinical signs of decreased response to FVIII administrations. Family history of inhibitors will not exclude the subject.

The following medical history exclusion criteria refer to tests performed by the central laboratory on samples collected at screening. Results must be reviewed prior to the Day 1 Advate dose to confirm eligibility:

7. Measurable inhibitor activity, using the Nijmegen-modified Bethesda assay, with ≥0.6 BU/mL considered a positive result.

8. VWF:RCo <50 IU/dL

9. Abnormal renal function, defined as serum creatinine >2.0 mg/dL.

10. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 × upper limit of normal (ULN).

11. Serum total bilirubin >3 × ULN.

Medications and Procedures

12. Previous participation in this study.

13. Current enrollment or participation within 30 days prior to screening in any other investigational study.

14. Treatment within 12 weeks prior to screening with a monoclonal antibody therapeutic, an Fc fusion protein other than rFVIIIFc, or IV immunoglobulin.

15. Vaccination within 30 days of screening.

16. Treatment with acetylsalicylic acid (ASA) within 2 weeks prior to screening or treatment with non-steroidal anti-inflammatory drugs (NSAIDs) at or above the maximum dose specified in the regional prescribing information for each product.

17. Systemic treatment within 12 weeks prior to screening with chemotherapy and/or other immunosuppressive drugs (except for the treatment of hepatitis C virus [HCV] or HIV). Use of corticosteroids is allowed, with the exception of systemic corticosteroid treatment given daily or on alternate days at 20 mg/day of prednisone or its equivalent for >14 days. Local, topical, and/or inhaled steroid use is permitted.

18. Major surgery within 8 weeks prior to screening or likely to require surgery during the study. Major surgery is defined as any surgical procedure (elective or emergent) that usually, but not always, involves general anesthesia and/or respiratory assistance, in which a major body cavity is penetrated and exposed, or a substantial impairment of physical or physiological functions is produced (e.g., laparotomy, thoracotomy, craniotomy, joint replacement, or limb amputation).

Other

19. Inability to comply with study requirements as assessed by the Investigator.

20. Other unspecified reasons that, in the opinion of the Investigator or Sponsor, make the subject unsuitable for enrollment.

9. SCREENING AND ENROLLMENT

9.1. Screening

Subjects (or their legally authorized representative, e.g., parent or legal guardian) must provide informed consent before any screening tests are performed, including washout of current therapy specifically for entry into the study (see Table 1 and Section 17.3). Subject assent must also be obtained if applicable in the site's geographic region. Participating study sites are required to document all screened candidates initially considered for inclusion in the study. Subjects will be registered as screened in the Interactive Response Technology (IRT) system following completion of all screening assignments.

The screening period for determination of subject eligibility for the study is scheduled within 28 days prior to Advate single-dose administration. Screening may be accomplished over the course of more than 1 study visit if needed. Additionally, the Screening Visit may be extended up to 120 days with prior Sponsor approval. If the Screening Period extends beyond 56 days, screening assessments must be repeated as specified in Table 1 prior to dosing with Advate. See Table 6 for washout instructions prior to the Advate dose. See Table 7 for instructions for treatment of bleeding, if applicable.

Screen failures are defined as subjects who sign the informed consent form (ICF) but are not subsequently dosed with Advate. If a subject is considered a screen failure, the reasons for exclusion must be documented in the subject's source documents and on the screening log. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs. Individuals who do not meet the criteria for participation in this study (i.e., a screen failure) will not be rescreened.

9.2. Enrollment

Subjects will be enrolled via IRT after all screening assessments have been completed and after the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. Subjects will be assigned a unique identification number that will be used on study-related documents pertaining to the subject, and will be administered their Advate dose (25 IU/kg or 65 IU/kg) on the day of their official enrollment in the study. Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment or withdraws from the study.

Refer to the Study Reference Guide for details on enrollment.

9.3. Blinding Procedures

Not applicable. This is an open-label study.

10. DISCONTINUATION OF STUDY TREATMENT AND WITHDRAWAL OF SUBJECTS FROM THE STUDY

Every effort will be made to keep subjects in the study; however, if a subject is withdrawn from the study early, the Investigator will make every effort to complete and report the reason(s) for withdrawal as thoroughly as possible.

The reason(s) for discontinuation of study treatment and withdrawal from the study must be recorded in the subject's case report form (CRF). Subjects who discontinue study treatment and withdraw from the study will not be allowed to enroll again at a later date.

Determination of whether a subject should discontinue further treatment and withdraw from the study will depend on whether a discontinuation criterion occurs prior to or after the subject received BIVV001.

Subjects who withdraw from the study may be replaced; refer to Section 10.1.3.

10.1. Withdrawal of Subjects From Study

10.1.1. Criteria for Subject Withdrawal From Study Prior to BIVV001 Administration

A subject must permanently discontinue further treatment and will be withdrawn from the study for any of the following reasons:

- The subject withdraws consent prior to receiving BIVV001.
- More than 1 bleeding episode occurs during the pre-Advate washout.
- More than 1 bleeding episode occurs between Advate and BIVV001 dosing.
- More than 28 days elapse as a result of a bleeding event between the Advate dose and the planned BIVV001 dose.
- Any of the following events occur before the BIVV001 dose:
  - The Investigator or Sponsor notes a significant noncompliance with protocol procedures.
  - The subject requires major surgery, as defined in the exclusion criteria.
  - The Investigator and/or Sponsor determines that the subject must discontinue further treatment due to an intolerable toxicity, a medical emergency, or other medical reasons.

Subjects who received Advate but discontinue treatment prior to receiving BIVV001 for reasons other than withdrawal of consent will be asked to participate in a post-Advate follow-up safety telephone call as part of the withdrawal from the study. If a subject who is withdrawn from the study has an ongoing SAE, the SAE should be followed until the event has resolved, stabilized, or returned to baseline status. Further details on actions for subjects who are discontinued from the study are provided in Table 5.

10.1.2. Criteria for Subject Withdrawal From Study After BIVV001 Administration

Once subjects receive BIVV001, they will be strongly encouraged to remain in the study to perform the remaining protocol-required assessments (PK sampling, inhibitor tests, and other safety assessments of the 28-day safety observation period and the EOS evaluations), unless they withdraw consent.

For any subjects who are withdrawn from the study prior to completion of the 28-day safety observation period (for reasons other than withdrawal of consent), EOS (Visit 15) procedures must be performed at the time of study withdrawal. If a subject who is withdrawn from the study has an ongoing SAE, the SAE should be followed until the event has resolved, stabilized, or returned to baseline status. Further details on actions for subjects who are withdrawn from the study are provided in Table 5.

10.1.3. General Considerations

Subjects who experience a discontinuation criterion or withdraw consent before completing adequate PK and/or inhibitor sampling for both Advate and BIVV001 will be replaced if needed to ensure that evaluable PK and FVIII inhibitor data are obtained from at least 6 subjects in the low-dose cohort and 8 subjects in the high-dose cohort.

10.2. Lost to Follow-Up

Subjects will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain whether the subject wishes to and/or should continue in the study.
- Should the subject be unreachable by telephone, the Investigator or designee must make every effort to regain contact with the subject. These contact attempts should be documented in the subject's medical record.

- In cases in which the subject is deemed lost to follow-up, then the subject will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

11. STUDY TREATMENT USE

Bioverativ will provide BIVV001 to all study sites; sites will be expected to procure their own supplies of Advate for use in the study. Section 12 provides summaries for storage, handling, preparation, disposal, and accountability information for both BIVV001 and Advate.

11.1. Regimen

Refer to Figure 1 for a schematic of study design and to Section 5 for study schedules.

All study visits will be performed as outpatient visits. All Advate and BIVV001 doses will be administered via slow, manual IV injections over a duration of 8 ± 2 minutes. Treatments will be administered by the Investigator or designated personnel at each study site, where emergency medical equipment must be readily available.

Details for each study cohort are listed below:

11.1.1. Regimen for Low-Dose Cohort (Advate and BIVV001 25 IU/kg Single Doses)

- Approximately 8 eligible, consenting subjects will undergo a screening period of up to 28 days (extendable to 120 days with prior Sponsor approval). If the Screening Period extends beyond 56 days, screening assessments must be repeated as specified in Table 1 prior to dosing with Advate. The screening period includes a washout period of 4 to 5 days without FVIII treatment. Prior to Advate dosing, a minimum of 4 days (96 hours) must have elapsed since the subject's last dose of conventional FVIII products. For subjects who were taking an EHL FVIII product, the washout period before Advate administration must be a minimum of 5 days (120 hours) (Table 1).

- Subjects will receive a single IV dose of Advate 25 IU/kg (Table 2).

- Subjects will complete a 72-hour PK sampling period at designated predose and postdose time points (Table 2).

- Subjects will complete a 72-hour washout period following Advate administration (this washout period may overlap with the PK sampling period; Table 6), then receive a single IV dose of BIVV001 25 IU/kg (Table 3).

- Following BIVV001 25 IU/kg single-dose administration, subjects will complete a 10-day PK sampling period at designated predose and postdose time points (Table 3).

- Following BIVV001 25 IU/kg single-dose administration, subjects will complete a 28-day (±5 days) safety observation period (Table 5). Please note that the first

10 days of this observation period overlaps with the 10-day PK sampling period (above).

Once the evaluation criteria for the low-dose cohort have been met, the Sponsor and the DSMC will review the data and determine if it is acceptable to proceed to the high-dose cohort as detailed in the DSMC charter.

11.1.2. Regimen for High-Dose Cohort (Advate and BIVV001 65 IU/kg Single Doses)

- Approximately 10 eligible, consenting subjects will undergo a screening period of up to 28 days (extendable to 120 days with prior Sponsor approval). If the Screening Period extends beyond 56 days, screening assessments must be repeated as specified in Table 1 prior to dosing with Advate. The screening period includes a washout period of 4 to 5 days without FVIII treatment. Prior to Advate dosing, a minimum of 4 days (96 hours) must have elapsed since the subject's last dose of conventional FVIII products. For subjects who were taking an EHL FVIII product, the washout period before Advate administration must be a minimum of 5 days (120 hours) (Table 1).

- Subjects will receive a single IV dose of Advate 65 IU/kg (Table 2).

- Subjects will complete a 72-hour PK sampling period at designated predose and postdose time points (Table 2).

- Subjects will complete a 96-hour washout period following Advate administration (this washout period may overlap with the PK sampling period; Table 6), then receive a single IV dose of BIVV001 65 IU/kg (Table 4).

- Following BIVV001 65 IU/kg single-dose administration, subjects will complete a 14-day PK sampling period at designated predose and postdose time points (Table 4).

- Following BIVV001 65 IU/kg single-dose administration, subjects will complete a 28-day (±5 days) safety observation period (Table 5). Please note that the first 14 days of this observation period overlaps with the 14-day PK sampling period (above).

11.2. Modifications of Dose and/or Treatment Schedule

11.2.1. Modifications to BIVV001 and/or Advate Doses

Doses will be calculated for each subject according to the subject's assigned dose of Advate or BIVV001 from the body weight obtained from the subject immediately prior to scheduled Advate and BIVV001 dose administrations (Table 2, Table 3, and Table 4).

11.2.2. Modifications to BIVV001 and/or Advate Dose Administration

11.2.2.1. Allergic Reactions

If any subject develops signs or symptoms of an allergic-type reaction during the administration of Advate or BIVV001, the injection will be immediately terminated and appropriate medical care will be initiated (if necessary). If the reaction occurs during Advate administration, the subject will be withdrawn from the study. If the reaction occurs during BIVV001 administration, PK assessments and the safety observation period should be completed, at the discretion of the Investigator. Refer to Table 5 and Section 10.1 for detailed information on subject withdrawal requirements.

11.2.2.2. Anaphylactic Reactions

If any subject develops signs or symptoms of an anaphylactic reaction during the administration of Advate or BIVV001, the injection will be immediately stopped, and appropriate medical care will be administered. If any signs or symptoms of shock are observed, the current medical standards of treatment should be administered. If the reaction occurs during Advate administration, the subject will be withdrawn from the study. If the reaction occurs during BIVV001 administration, PK assessments and the safety observation period should be completed, at the discretion of the Investigator. Refer to Table 5 and Section 10.1 for detailed information on subject withdrawal requirements.

11.2.2.3. Bleeding Episodes

Refer to Table 7 for instructions on appropriate responses to bleeding episodes.

11.2.3. Modifications to Treatment Schedule

See Section 7.1 for details regarding the study's stepwise dosing and dose escalation procedures.

11.3. Precautions

BIVV001 is being administered for the first time to humans; thus, all subjects will be observed closely for safety following administration of BIVV001 as described in Sections 7.1, 14, and 15. Whether and which side effects may occur is unknown. Clinical safety data are available for commercially available rFVIII products, including Advate [Advate USPI 2015; Adynovate USPI 2016; Eloctate USPI 2017].

11.3.1. Bleeding Episodes

As this is a safety and PK study, the doses of Advate and BIVV001 being administered are not intended to provide the subject optimal protection from new bleeding episodes. Refer to Table 7 for detailed instructions on the treatment of bleeding episodes that occur during this study. Bleeding episodes will be reported on the CRF.

11.4. Compliance

All doses of Advate and BIVV001 will be administered by study site staff.

11.5. Concomitant Therapy and Procedures

11.5.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between the time that the subject is enrolled in the study and the end of the 28-day safety observation period.

11.5.1.1. Allowed Concomitant Therapy

If a subject requires treatment for a bleeding episode during the study, the subject's prestudy FVIII product should be used for treatment. Refer to Table 7 for instructions on appropriate responses to bleeding episodes. Subjects are also permitted to resume their prestudy FVIII regimen after completion of Visit 14 activities (see Table 3 and Table 4).

It is preferred for this study not to include subjects requiring concomitant medications. However, subjects taking medication routinely for a pre-existing condition should be on a regimen that has been stable for at least 3 weeks, and dosage changes should not be anticipated during the observation period for this study. Prestudy stable NSAID doses below the maximum dose specified in the regional prescribing information at the time of enrollment are permitted. All concurrent prescription and non-prescription medications including over-the-counter and alternative preparations (including herbal remedies, vitamins, and health food supplements) should be recorded at baseline and throughout the treatment and follow-up periods.

11.5.1.2. Disallowed Concomitant Therapy

No FVIII injections are permitted within 4 days prior to the injection of Advate or BIVV001.

No premedication for pain or pyrexia relief are to be administered for injections of the drugs. Should premedications be contemplated, this will be discussed on a case-by-case basis with the Medical Monitor and the Sponsor's Clinical Operations representative before administration.

With the exception of a subject resuming prestudy FVIII regimen after the completion of all Visit 14 activities (Section 11.5.1.1), no drugs interfering with hemostasis (such as tranexamic acid, warfarin, and heparin), experimental drugs, blood products (such as red blood cells [RBCs], platelets, and fresh frozen plasma), and drugs affecting immune function (such as interferon, ribavirin, immunizations, systemic steroids, and chemotherapy) may be taken during the subject's participation in this study; subjects requiring such medications and/or products will be discontinued from the study (Section 10). Acetylsalicylic acid is not allowed. Non-steroidal anti-inflammatory drugs [NSAIDs] at or above the maximum dose specified in the regional prescribing information for each product are not allowed.

11.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the time that the subject is enrolled in the study and the end of the 28-day safety observation period.

11.5.3. Recording of Concomitant Therapies and/or Procedures

The use of concomitant therapies or procedures (defined in Section 11.5.1 or Section 11.5.2) must be recorded on the subject's CRF according to the instructions for its completion. Any AEs related to administration of these therapies or procedures must be documented on the appropriate CRF.

11.6. Continuation of Treatment

There is no provision to provide additional treatment with Advate or BIVV001 after the study.

12. STUDY TREATMENT MANAGEMENT

12.1. BIVV001

BIVV001 drug product will be supplied as [redacted] which will also be supplied by Bioverativ. For this study, each vial of drug product includes 1000 IU of BIVV001 along with the following excipients: [redacted]. Please refer to the BIVV001 Directions for Handling and Administration (DHA) or BIVV001 IB for additional details.

BIVV001 will be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice. BIVV001 vials will be labeled according to the requirements of local law and legislation. Label text will be approved according to Bioverativ procedures, and copies of the labels will be made available to the study site upon request.

Study site staff should follow the BIVV001 DHA for specific instructions on its storage, handling, preparation, administration, disposal, and accountability.

BIVV001 must be dispensed only by a pharmacist or appropriately qualified staff. BIVV001 is to be dispensed only to subjects enrolled in this study. Once BIVV001 is prepared for a subject, it can be administered only to that subject. BIVV001 doses will be administered by the Investigator or designated personnel at each study site, where emergency medical equipment must be readily available. BIVV001 preparations are for one-time use only; study site staff should not use any leftover BIVV001 remaining in the vial for another subject.

Accountability for BIVV001 is the responsibility of the Investigator. The study site must maintain accurate records demonstrating dates and amount of BIVV001 received, to whom dispensed (subject-by-subject accounting), and accounts of any BIVV001 accidentally or deliberately destroyed or lost. Unless otherwise notified, all BIVV001 vials (used and unused) must be saved for BIVV001 accountability. By the end of the study, reconciliation must be made between the amount of BIVV001 supplied, dispensed, and subsequently destroyed, lost, or returned to Bioverativ. A written explanation must be provided for any discrepancies.

12.2. Advate

Advate is available as a lyophilized powder in single-use vials containing nominally 250, 500, 1000, 1500, 2000, 3000, or 4000 IU. The 250 to 1500 IU strengths come with 2 mL of Sterile Water for Injection; the 2000 to 4000 IU strengths come with 5 mL of Sterile Water for Injection.

Study site staff should follow the regional product label for Advate for instructions on its storage, preparation, administration, handling, disposal, and accountability requirements.

13. EFFICACY AND PHARMACOKINETIC ASSESSMENTS

See Section 5 for the timing of all assessments.

Tests and evaluations affecting endpoints and/or analyses may need to be repeated if the original results are lost or damaged. Duplicate samples for key laboratory assessments will be collected as a backup in case the original sample is lost or not evaluable. In cases where duplicate samples are no longer available, subjects may be asked to return to the clinic to repeat the evaluations.

13.1. Clinical Efficacy Assessments

No formal clinical efficacy assessments will be performed.

13.2. Laboratory Efficacy Assessments

No formal laboratory efficacy assessments will be performed. However, the PK evaluation will provide an initial understanding of the efficacy of BIVV001 in humans, consistent with the view from the European Medicines Agency (EMA) guidelines that PK data are considered the most important surrogate markers for efficacy of a new FVIII product [EMA 2016].

13.3. Pharmacokinetic Assessments

One-stage (aPTT-based) clotting assay and two-stage chromogenic coagulation assays will be performed to assess FVIII activity (referred to as PK) following both Advate and BIVV001 administration. The PK of BIVV001 single dose will be assessed and compared to that of Advate single dose via the estimation of parameters including but not limited to the following: C_{max}, $t_{½}$, CL, V_{ss}, AUC_{∞}, MRT, IR, and time to 1% above baseline for FVIII activity.

Pharmacokinetics sampling schedules for Advate administration, BIVV001 25 IU/kg administration, and BIVV001 65 IU/kg are presented in Table 2, Table 3, and Table 4, respectively.

13.4. Pharmacodynamic Assessments

No pharmacodynamic assessments are planned for this study.

13.5. Pharmacogenetic and Genetic Assessments

Where local regulations and EC approval allow, an optional sample will be collected at screening for genotype analysis, including [redacted], to aid in interpreting the potential risk of inhibitor development. The sample will not be needed if previously documented. Collection of samples and previously documented genotype information for genotype analysis will be governed by a separate ICF; genotype will not be a criterion for inclusion or exclusion.

The DNA samples will be coded with the subject's identification number and stored for 15 years or a duration dictated by local, national, or regional laws or regulations. No genotyping or genetic data will be provided to the subject. Subjects may withdraw consent and request to have their sample destroyed at any time and no further genetic data will be generated; any data already generated will not be destroyed.

13.6. Exploratory Assessment

[redacted]

14. SAFETY ASSESSMENTS

Refer to Section 5 for the timing of all safety assessments.

Tests and evaluations affecting endpoints and/or analyses may need to be repeated if the original results are lost or damaged. Duplicate samples for key laboratory assessments will be collected as a backup in case the original sample is lost or not evaluable. In cases where duplicate samples are no longer available, subjects may be asked to return to the clinic to repeat the evaluations.

The total estimated blood sample volume collected from a subject will not exceed approximately 87 mL at one time and 330 mL over the duration of the study.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of BIVV001:

- Medical, surgical, and hemophilia history
- Physical examinations
- Vital sign measurements: systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature. Vital sign measurements should be taken after the subject has been resting (supine position) for at least 5 minutes. Postdose vital sign measurements should be taken before PK sample collection. Vital signs should also be taken at any unscheduled visit.
- Body weight measurements. On Advate and BIVV001 dosing days (Visits 2 and 6, respectively), body weight measurements will be used to calculate the Advate and BIVV001 doses to be prepared and administered.
- Concomitant therapy and procedure recording
- AE and SAE recording.

14.2. Laboratory Safety Assessments

Samples will be analyzed using Good Laboratory Practice-validated assays.

The following laboratory assessments will be performed to evaluate the safety profile of BIVV001:

- Hematology: red blood cell (RBC) count; white blood cell (WBC) count and differential; platelet count; hemoglobin (Hgb); and hematocrit (Hct)
- Clinical chemistry: alanine aminotransferase (ALT); aspartate aminotransferase (AST); alkaline phosphatase (ALP); gamma-glutamyl transferase (GGT); bilirubin;

blood urea nitrogen (BUN); creatinine; glucose; total protein; sodium; potassium; and chloride

- Urinalysis: specific gravity; pH; color; appearance; leukocyte esterase; protein; glucose; ketones; occult blood; bilirubin; urobilinogen; nitrite; and microscopic examination of urine sediment

- Coagulation and thrombosis markers: prothrombin time (PT); aPTT; D-dimer; international normalized ratio; thrombin anti-thrombin complex; prothrombin fragment 1.2; and the von Willebrand comprehensive panel, which includes assessments of VWF ristocetin cofactor activity, and VWF antigen. Analysis of VWF multimers will be for future testing.

- Detection of FVIII inhibitors, as determined by the Nijmegen-modified Bethesda assay. A subject's blood will be considered to be positive for FVIII inhibitor when an initial test result of ≥0.6 BU/mL is identified and confirmed by a subsequent test result from an independent blood sample collected within 2 to 4 weeks of the first positive sample.

14.3. Immunogenicity Assessments

Blood samples will be collected for the detection and analysis of anti-rFVIIIFc-VWF-XTEN antibodies at the following visits:

- Screening visit (Visit 1) and, if necessary, Repeat Screening Visit

- Advate dosing visit (Visit 2) – sample collected predose

- BIVV001 dosing visit (Visit 6) – sample collected predose

- 14-day inhibitor visit (Visit 14) – this visit must occur 336 ± 24 hours after BIVV dose administration

- EOS visit (Visit 15) or ET visit.

Testing for potential antibody formation will be performed at a central laboratory using a validated rFVIIIFc-VWF-XTEN-specific anti-drug antibody assay. Confirmed positive samples will be further characterized for antibodies specific to Fc, FVIII, D′D3, or XTEN.

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject (or his legally authorized representative and/or main caregiver) must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Serious Pretreatment Event

A serious pretreatment event (PTE) is any event that meets the criteria for SAE reporting (as defined in Section 15.1.3), occurs after the subject signs the ICF, but occurs before the administration of Advate or BIVV001.

15.1.2. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Determination of whether an abnormal laboratory value and/or vital sign result meets the definition of an AE will be made by the Investigator. Abnormal results are not considered AEs unless one or more of the following criteria are met:

- The result meets the criteria for an SAE
- The result requires the subject to receive specific corrective therapy
- The result is considered by the Investigator or the subject's treating hematologist to be clinically significant

Bleeding episodes in this patient population are not considered AEs; however, the concomitant events associated with a bleeding episode should be reported as AEs as appropriate (e.g., an elbow fracture). Bleeding episodes that meet a serious criterion (Section 15.1.3) should be reported as an SAE.

15.1.3. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is a medically important event

A medically important event is an AE that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.3
- The relationship of the event to study treatment as defined in Section 15.2.2
- The severity of the event as defined in Section 15.2.3

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

Relationship of Event to Study Treatment	
Not related	An AE will be considered "not related" to the use of the investigational product if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include but are not limited to the lack of reasonable temporal relationship between administration of the investigational product and the AE, the presence of a biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the use of the investigational product if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include but are not limited to a positive rechallenge, a reasonable temporal sequence between administration of the investigational product and the AE, a known response pattern of the suspected product, improvement following discontinuation or dose reduction, a biologically plausible relationship between the product and the AE, or a lack of an alternative explanation for the AE.

15.2.3. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptoms barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms but may be given because of personality of subject.
Moderate	Symptoms of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptoms may be needed.
Severe	Symptoms cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptoms may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by Bioverativ according to the BIVV001 IB.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time that they sign the ICF through the end of the 28-day safety observation period is to be recorded on the CRF, regardless of the severity of the event or its relationship to Advate or BIVV001. At each study visit, the Investigator will assess the subject for AEs and will record any new AEs or updates to previously reported AEs on the CRF.

All AEs experienced by the subject should be followed until they have resolved, stabilized, or returned to baseline in subsequent visits.

15.3.2. Serious Adverse Events

Any SAE experienced by the subject between the time of the signing of the ICF and the end of the 28-day safety observation period is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to IQVIA Pharmacovigilance within 24 hours as described in Section 15.3.3. Follow-up information regarding an SAE also must be reported within 24 hours.

Subjects will be followed for all SAEs until the end of the 28-day safety observation period. Thereafter, the event should be reported to IQVIA Pharmacovigilance only if the Investigator considers the SAE to be related to study treatment.

Any SAE that is ongoing when the subject completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

In this study, the following events are considered medically important and must be reported as SAEs:

- A subject develops an inhibitor (Section 7.6.1)
- A subject develops a Grade 2 or greater allergic reaction in association with administration of BIVV001 defined as follows using the Recommendations for Grading of Acute and Subacute Toxic Effects on the World Health Organization (WHO) scale [WHO 1979]:
  - Grade 2: bronchospasm, no parenteral therapy needed
  - Grade 3: bronchospasm, parenteral therapy required
  - Grade 4: anaphylaxis
- A subject develops a vascular thrombotic event, with the exception of IV injection site thrombophlebitis.

Allergic reactions, including anaphylaxis, have been reported with FVIII products. The subject (and the subject's parents/caregivers, if applicable) should be informed of early symptoms and signs of hypersensitivity reactions, including difficulty breathing, chest tightness, swelling of the face, rash, or hives. If such an event occurs while the subject is at home, the subject will be instructed to seek immediate medical care.

The subject (and the subject's parents/caregivers, if applicable), should be informed of early symptoms and signs of thrombotic phenomena, including pain and/or tenderness along a vein, unexpected swelling of an arm or leg without pain or tenderness, redness along a vein, low fever without any known reason (such as a cold or flu), sudden shortness of breath or difficulty breathing, or coughing, sudden chest pain, sudden severe headache or changes in vision, and numbness or tingling in arms or legs. If such an event occurs while the subject is at home, the

subject (and the subject's parents/caregivers, if applicable) will be instructed to seek immediate medical care.

15.3.3. Immediate Reporting of Serious Adverse Events

To adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify IQVIA Pharmacovigilance within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

A report ***must be submitted*** to IQVIA Pharmacovigilance regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not the subject has received study treatment
- The severity of the event
- The relationship of the event to study treatment

To report initial or follow-up information on an SAE, fax or email a completed SAE form; refer to the Study Reference Guide for complete contact information.

Any SAE must also be entered in the CRF in the same time frame.

15.3.3.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to IQVIA Pharmacovigilance. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Bioverativ to be related to the study treatment administered. Bioverativ (or designee) will report SUSARs to the appropriate regulatory authorities and Investigators as required, according to local law.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

The population under study is male; therefore, pregnancies will not be tracked. Congenital abnormalities and birth defects in the offspring of male subjects should be reported as an SAE if conception occurred during the study treatment period.

15.4.2. Overdose

An overdose is any dose of study treatment administered to a subject or taken by a subject that exceeds the dose assigned to the subject according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on an Overdose form and faxed or emailed to IQVIA Pharmacovigilance within 24 hours of the site becoming aware of the overdose. An overdose must be reported to IQVIA Pharmacovigilance even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed or emailed to IQVIA Pharmacovigilance. All study treatment-related dosing information must be recorded on the dosing CRF.

15.4.3. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator (or designee) should contact the study's Medical Director. Refer to the Study Reference Guide for complete contact information.

15.4.3.1. Unblinding for Medical Emergency

Not applicable, as this is an open-label study.

15.5. Contraception Requirements

There are no contraception requirements for this study.

15.6. Safety Responsibilities

15.6.1. Investigator Responsibilities

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, on the CRF regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.

- Complete an SAE form for each SAE and fax or email it to IQVIA Pharmacovigilance within 24 hours of the study site staff becoming aware of the event.

- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to IQVIA Pharmacovigilance within 24 hours of the study site staff becoming aware of new information.

- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.

- Pursue AE follow-up information until the event has resolved or become stable. Record AE follow-up information, including resolution, on the CRF, as applicable.

- Report SAEs to local ECs, as required by local law.

15.6.2. Bioverativ Responsibilities

Bioverativ's responsibilities include the following:

- Before a site can enroll any subjects, the Clinical Monitor or the Sponsor's designee is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.

- Bioverativ is to notify all appropriate regulatory authorities, central ECs, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

16.1. Description of Objectives and Endpoints

The objectives of the study and the endpoints to be analyzed are described in Section 6.

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan. In general, unless otherwise stated, continuous variables will be summarized by descriptive statistics, including: number, mean, median, standard deviation, minimum, and maximum. Categorical variables and response variables will be presented with the number and percentage in each category. Additionally, exploratory statistical tests may be applied to study data to generate hypotheses to be tested in subsequent trials.

16.2. Demographics and Baseline Disease Characteristics

Demographic and other baseline disease characteristics will be summarized using descriptive statistics by dose level and overall. Number of observations, mean, standard deviation, median, minimum, and maximum will be presented for continuous parameters. Categorical parameters will be displayed using counts and percentages within each category. Data to be tabulated will include, but not be limited to, age, race, medical history, and other disease specific measures. All data will be summarized by drug and dose level group.

16.3. Efficacy

No formal clinical efficacy assessments will be performed.

16.4. Pharmacokinetics

16.4.1. Analysis Population

The PK analysis set is defined as all subjects who complete the relevant blood sample collections (following Advate or BIVV001 administration), enabling acceptable determination of all key PK parameters, as determined by the PK scientist.

16.4.2. Methods of Analysis

In general, descriptive statistics including number of observations, mean, standard deviation, median, minimum, and maximum will be presented for continuous parameters. Summary descriptive statistics and individual subject listings will be presented for all PK parameters (listed in Section 6.2) by drug and dose level group. Various exploratory statistical tests may be applied to study data to generate hypotheses to be tested in subsequent trials.

FVIII activity-versus-time profiles will be plotted for each subject, and mean activity-versus-time profiles will be plotted at each dose level for BIVV001 and Advate for the one-stage clotting assays and chromogenic assays, on both the linear and logarithmic scale. Individual PK parameter estimates will be listed for each subject and summarized descriptively by drug and dose level group for both assays. Summary descriptive statistics will include the number of observations, arithmetic and geometric means and their associated confidence intervals (CIs), standard deviation, coefficient of variation, median, minimum, and maximum.

An analysis of variance model with factors for drug and subject will be used to compare BIVV001 to Advate for the analysis of selected PK parameters, including but not limited to C_{max}, $t_{½}$, CL, V_{ss}, AUC_{∞}, MRT, IR, and time to 1% above baseline for FVIII activity. Analyses will be performed for each dose level separately. PK parameters will be log-transformed for these analyses, and estimated means, mean differences, and CIs on the log scale will be exponentiated to obtain estimates for geometric means, geometric mean ratios, and CIs, respectively, on the original scale. In addition, untransformed PK parameters will be used to calculate arithmetic means and arithmetic mean ratios.

16.5. Pharmacodynamics

No pharmacodynamics assessments are planned for this study.

16.6. Biomarker Analyses/Pharmacogenetics

No biomarker analyses or pharmacogenetics assessments are planned for this study.

16.7. Safety

16.7.1. Analysis Population

All subjects who receive at least 1 dose of Advate or BIVV001 will be evaluable for the analysis of safety.

16.7.2. Methods of Analysis

Adverse events will be classified using Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Tabulations of AEs by frequency, relatedness, and severity will be presented. Data will be presented for each drug and by dose level group. Subject listings will be provided for SAEs.

Changes from baseline in clinical laboratory parameters and vital signs will be summarized over time using descriptive statistics for each drug and dose level group.

16.8. Immunogenicity

16.8.1. Analysis Population

All subjects who receive at least 1 dose of Advate or BIVV001 will be evaluable for the analysis of immunogenicity.

16.8.2. Methods of Analysis

The number and percentage of subjects who are positive at the end of the study for inhibitor and anti-rFVIIIFc antibodies will be presented for each drug and by dose level group.
All inhibitor and antibody data will also be listed by subject.

16.9. Interim Analyses

No formal interim analyses are planned. At least one interim analysis is planned at the conclusion of the low-dose cohort and will be descriptive in nature.

Additional analyses may be performed to support dose regimen planning for future studies.

16.10. Sample Size Considerations

The sample size for this study is based on the need to establish the initial safety profile of BIVV001 and characterize its PK profile. The number of subjects who have severe hemophilia A is small; thus, the determination of sample size for this study is constrained by subject availability. Approximately 18 subjects will be enrolled and treated. Additional subjects may be enrolled to ensure that at least 6 subjects from the low-dose cohort and 8 subjects from the high-dose cohort provide evaluable PK (defined in Section 16.4.1) and inhibitor data.

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17. ETHICAL REQUIREMENTS

Bioverativ, IQVIA, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines, and conduct the study according to local regulations.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated. The Investigator is responsible for supervising those individuals and for implementing procedures to ensure the integrity of the tasks performed and any data generated.

17.1. Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

17.2. Ethics Committee

The Investigator must obtain EC approval of the protocol, ICF, and other required study documents prior to starting the study. IQVIA will submit documents on behalf of the investigational sites in countries other than the US.

If the Investigator makes any changes to the ICF, Bioverativ must approve the changes before it is submitted to the EC. A copy of the approved ICF must be provided to Bioverativ. After approval, the ICF must not be altered without the agreement of the relevant EC and Bioverativ.

It is the responsibility of the Investigators to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

Bioverativ must receive a letter documenting EC approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the EC at required intervals and not less than annually.

At the completion or termination of the study, the investigational site must submit a close-out letter to the EC and Bioverativ.

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject

or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject (or the subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

Subjects will be informed that their race and ethnicity will be collected and will be used during analysis of study results. A copy of the signed and dated ICF or assent must be given to the subject or the subject's legally authorized representative. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs. Confirmation of informed consent or assent must also be documented in the subject's medical record.

17.4. Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., Protected Health Information authorization in North America).

The race and ethnicity of subjects will be collected in this study. These data may be used in the analysis of the safety and/or PK profile of the study treatment. In previous cross-sectional analyses of different ethnic groups, differences in the occurrence of FVIII inhibitors have been observed [Astermark 2005; Carpenter 2012]. Additionally, differential responses to FVIII products may occur in different haplotypes of FVIII that also differ across racial and ethnic groups [Viel 2009].

Study reports will be used for research purposes only. The subject will not be identified by name in CRFs, study-related forms, study reports, or any related publications. Bioverativ, its partners and designees, ECs, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

17.5. Compensation for Injury

Bioverativ maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in Bioverativ or IQVIA) with the subject before the subject makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

Bioverativ will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, which will be conducted by IQVIA. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Control and Quality Assurance

Quality control procedures will be implemented at each stage of data handling to ensure that all data are reliable and have been processed correctly. Data anomalies will be communicated to the sites for clarification and resolution, as appropriate.

During and/or after completion of the study, quality assurance officers named by Bioverativ or the regulatory authorities may wish to perform onsite audits or inspections. The Investigator will be expected to cooperate with any audit or inspection and to provide assistance and documentation (including source data) as requested.

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories. Source data must be attributable, legible, original, accurate, contemporaneous, and complete. Changes to source data must be traceable, not obscure the original entry, and be explained if necessary (e.g., with an audit trail). The Investigator should maintain a record of the location(s) of essential documents.

The Clinical Monitor will visit the study site at regular intervals during the study and after the study has completed, as appropriate. A clinical site monitoring plan will detail who performs the monitoring, how often, and the extent of review. It also will provide the monitoring strategy, with emphasis on subject safety, data integrity, and critical data and processes. During such visits, CRFs, supporting documentation, and essential documentation related to the study will be reviewed and any discrepancies or omissions will be resolved. Remote evaluation of data (centralized monitoring) may also be conducted and reported as defined in the monitoring plan.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure the protection of subject rights and well-being, protocol adherence, quality of data (accurate, complete, and verifiable), study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

Bioverativ is the Sponsor of the study and is funding the study. All financial details are provided in the separate contracts between the institution, Investigator, and Bioverativ.

18.5. Publications

Details are included in the clinical trial agreement for this study.

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

Bioverativ will ensure oversight of any study-related duties and functions carried out on its behalf and will specify in writing all duties and functions that are transferred.

19.1.1. Contract Research Organization

IQVIA will be responsible for administrative aspects of the study, including but not limited to study initiation (including review of study responsibilities with study site Investigators and staff), monitoring, management of SAE reports, and data management. Contract research organizations will be used to prepare and publish the clinical study report.

19.1.2. Interactive Response Technology

Interactive response technology (IRT) will be used in this study. Before subjects are screened or enrolled, the IRT vendor or Sponsor designee will provide each study site with the necessary training, a user manual, and access rights to the system. Specific details regarding the IRT system are provided in the Study Reference Guide.

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a web-based electronic data capture tool developed and supported by IQVIA and configured by Bioverativ. It is recommended that data be entered into the electronic data capture system within 5 business days, including batched records and records with source documents.

19.1.4. Central Laboratories for Laboratory Assessments

Central laboratories have been selected by Bioverativ to analyze all laboratory samples being collected for this study. Specifics regarding the requirements for laboratory specimen collection, handling, and analysis are provided in the Study Laboratory Manual, which is part of the Study Reference Guide.

19.1.5. Central Facility for Other Assessments

LabCorp (which includes Covance and Esoterix) has been selected by Bioverativ as the central laboratory for this study.

19.2. Study Committees

19.2.1. Data Safety Monitoring Committee

An independent DSMC will evaluate the safety data from the study on an ongoing basis. The DSMC and the Sponsor will also evaluate safety data to determine whether it is appropriate to escalate from the low-dose BIVV001 cohort to the high-dose BIVV001 cohort. The specifics regarding the DSMC organization and procedures will be outlined in a DSMC charter.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the EC and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the investigational scope, or the scientific quality of the study must be approved by the EC before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency before implementation. However, Bioverativ may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (refer to Sections 17.2 and 17.3).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the regulatory authorities and ECs must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local, national, or regional laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Bioverativ in writing and receive written authorization from Bioverativ to destroy study records. In addition, the Investigator must notify Bioverativ of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

Bioverativ will designate one or more of the participating Investigators as a signatory for the study report. This determination will be made by several factors, including but not limited to, the Investigator's experience and reputation in the studied indication; the Investigator's contribution to the study in terms of design, management, and/or subject enrollment; or by other factors determined to be relevant by Bioverativ.

Bioverativ will follow all applicable local regulations pertaining to study report signatories.

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Phase 1/2a, Open-Label, Dose-Escalation Study to Determine the Safety, Tolerability, and Pharmacokinetics of a Single Intravenous Injection of rFVIIIFc-VWF-XTEN (BIVV001) in Previously Treated Adults with Severe Hemophilia A," and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)