NCT03205163

STATISTICAL ANALYSIS PLAN

VERSION: 1.0
DATE OF PLAN:

13 APRIL 2018

BASED ON:

Protocol Version 6.0, dated 02 January 2018

STUDY DRUG:

rFVIIIFc-VWF-XTEN

PROTOCOL NUMBER:

242HA101

STUDY 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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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate transferase
aPTT	Activated partial thromboplastin time
AUC	Area under the concentration-time curve
ANOVA	Analysis of variance
BMI	Body mass index
CI	Confidence interval
CL	Clearance
C_{max}	Maximum activity
CV	Coefficient of variance
DSMC	Data Safety Monitoring Committee
eCRF	Electronic case report form
EMA	European Medicines Agency
FAS	Full analysis set
FVIII	Factor 8
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human immunodeficiency virus
kg	kilogram
IR	Incremental recovery
IU	International unit
IV	Intravenously
MedDRA	Medical Dictionary for Regulatory Activities Terminology
MRT	Mean residence time
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
PT	Prothrombin time
PTP	Previously treated patients
rFVIII	Recombinant factor 8
SD	Standard deviation

SAE	Serious adverse event
SAP	Statistical analysis plan
TEAE	Treatment-emergent adverse event
VWF	von Willebrand factor
V_{ss}	Volume of distribution at steady state

1. INTRODUCTION

This first-in-human study will evaluate the safety and tolerability of a single dose of BIVV001 administered intravenously (IV) in subjects with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII). In addition, this study will provide data on the pharmacokinetics (PK) of this drug compared with that of a commercially available recombinant FVIII (rFVIII) product (Advate).

This statistical analysis plan (SAP) describes the planned data summaries and statistical analyses to be performed for this study based on Protocol 242HA101 Version 6.0, dated 02 January 2018.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

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

2.1.2. Secondary Objective(s)

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

2.1.3. Exploratory Objective(s)

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

2.2. Study Endpoints

2.2.1. Primary Endpoint

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

Details of the analysis of primary endpoints are described in Section 9.

2.2.2. Secondary Endpoint(s)

The secondary endpoints are PK parameters based on the one-stage ([aPTT]-based) clotting assay, including but not limited to the following:

- maximum activity (C_{max}), half-life, clearance (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), incremental recovery (IR), and time to 1% above baseline for FVIII activity

Details of the analysis of secondary endpoints are described in Section 8.

2.2.3. Exploratory Endpoint(s)

The exploratory endpoints are PK parameters based on the two-stage chromogenic assay, including but not limited to the following:

- C_{max}, half-life, CL, V_{ss}, AUC_{∞}, MRT, IR, and time to 1% above baseline for FVIII activity

Details of the analysis of exploratory endpoints are described in Section 8.

3. STUDY DESIGN

3.1. Overall Study Design

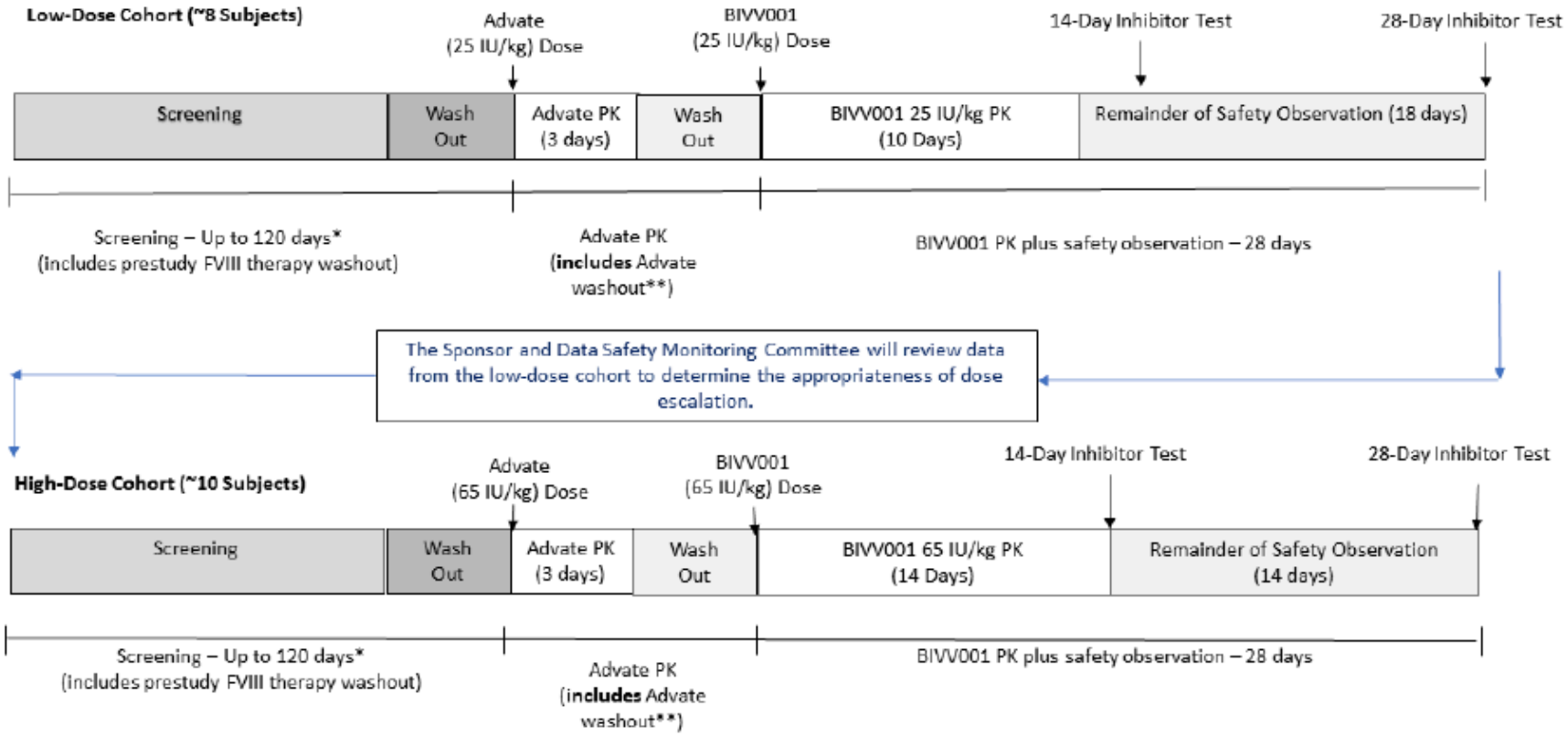
This is a Phase 1/2a, open-label, dose-escalation, multicenter study designed to evaluate the safety, tolerability, and PK of a single IV dose of BIVV001 in subjects with severe hemophilia A who have received at least 150 exposure days of prior FVIII treatment.

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 a 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. Subjects may resume treatment with their pre-study FVIII product during the 28-day observation period after completing Visit 14 activities (which include the 14-day inhibitor test). Only subjects with adequate samples for PK and inhibitor characterization following both Advate and BIVV001 dosing will be considered 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.

An independent Data Safety Monitoring Committee (DSMC) will evaluate the safety data from the study on an ongoing basis.

Figure 1: Study Schema



* 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 the protocol prior to dosing with Advate. Washout duration at least 96 hours (4 days) from the most recent FVIII dose (prestudy FVIIII) 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.

3.2. Statistical Hypothesis

No formal statistical hypothesis will be tested.

3.3. 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 and inhibitor data.

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3.4. Randomization and Blinding

This is an open-label study with no blinding or randomization.

3.5. Interim Analysis

No formal interim analyses are planned.

At least one interim analysis will be performed when at least 3 subjects in the low dose cohort have completed the 28-day safety observation period and have available safety and PK data.

This analysis will focus on baseline demographic information, adverse events, and pharmacokinetic data and will be of a descriptive nature. No formal hypothesis testing will be performed.

The DSMC will review safety summaries and listings on a quarterly interval as well as on an ad hoc basis, as needed. In addition, the DSMC will evaluate available data following the low dose cohort to determine the appropriateness of escalating to the high dose cohort once the following conditions have been met: a) inhibitor test results from samples collected 14 days after the BIVV001 injection are available for at least 6 of the 8 subjects in the low-dose cohort, and b) adequate PK sampling following the BIVV001 dose has been completed and safety assessment results through the end of PK sampling are available for all active subjects in the low-dose cohort. Further details are provided in the DSMC charter.

Other descriptive interim analyses may be performed as necessary to support dose regimen planning for future studies.

4. ANALYSIS POPULATIONS

4.1. All-Enrolled Analysis Set

The All-Enrolled Analysis Set is defined as all subjects who are enrolled into the study and have been assigned a unique subject identification number.

4.2. Safety Analysis Set

The Safety Analysis Set is defined as all subjects who receive at least one dose of Advate or BIVV001.

4.3. Pharmacokinetic Analysis Set (PKAS)

The Pharmacokinetic Analysis Set (PKAS) is defined as subjects who have adequate blood sample collections (following Advate or BIVV001 administration), to assess key PK parameters, as determined by the PK scientist.

5. DEFINITIONS AND DATA HANDLING

Statistical analysis is being performed by Bioverativ, using SAS® version 9.4 or higher and, where appropriate, additional validated software.

5.1. General Principles

In general, the following approaches will be used in the analysis and summary of safety and PK endpoints, unless otherwise specified in this SAP.

Safety and PK data will be summarized using standard summary statistics for continuous and categorical data. Data will be summarized by study drug and dose level.

Data collected at unscheduled visits will be excluded from analysis, unless otherwise specified. However, all analysis data, including data collected at unscheduled visits, will be listed in the subject data listings.

No statistical hypothesis testing is planned.

5.1.1. Definitions

5.1.1.1. Screening Period

The screening period starts after signing the study consent form and ends immediately prior to the first dose of Advate or BIVV001.

5.1.1.2. Advate Dosing and PK Profile Period

The Advate dosing and PK profile period is defined as the period starting at the dose of Advate and ending at the last Advate PK sampling time point.

5.1.1.3. BIVV001 Dosing and PK Profile Period

The BIVV001 dosing and PK profile period is defined as the period starting at the dose of BIVV001 and ending at the last BIVV001 PK sampling time point.

5.1.1.4. Safety Observation Period During Advate Treatment

The safety observation period during Advate treatment starts at the single dose administration of Advate and ends immediately prior to the single dose administration of BIVV001.

5.1.1.5. Safety Observation Period During BIVV001 Treatment

The safety observation period during BIVV001 treatment starts at the single dose administration of BIVV001 and ends at the 28-day visit or time of early withdrawal. Subjects may resume treatment with their pre-study FVIII product during the 28-day safety observation period after completing Visit 14 activities (which include the 14-day inhibitor test).

5.1.1.6. Safety Observation Period During Pre-study FVIII Product Use

The safety observation period during pre-study FVIII product use starts at the first dose of pre-study FVIII product during the BIVV001 Treatment Period and ends at the 28-day visit or time of early withdrawal.

5.1.1.7. Major Surgical Period

The major surgical period starts at the date and time of the major surgery and ends at the date and time that routine prophylaxis is resumed. If there is no record for routine prophylaxis after the date of major surgery, then the major surgical period will end at the hospital discharge date.

5.1.1.8. Study Day

Study day is defined as the number of days relative to the date of first dose of study drug and starts on Day 1. Study day will be calculated relative to the Advate dose date as well as the BIVV001 dose date.

Study day relative to the Advate dose will be calculated as (date of event – date of Advate administration + 1). If a repeat Advate dose is administered, study day relative to the Advate dose will be calculated based on the first Advate dose administered.

Study day relative to the BIVV001 dose will be calculated as (date of event – date of BIVV001 administration + 1).

For laboratory data, days from treatment is calculated as (sample collection date – date of Advate administration) for the Screening period; (sample collection date – date of Advate administration + 1) for the Advate treatment period; and (sample collection date – date of BIVV001 administration + 1) for the BIVV001 treatment period.

Incomplete dates will be imputed for the calculation of study days, unless specified otherwise:

- If missing day only, the start date will be imputed as the first day of the month, while the end date will be imputed as the last day of the month
- If missing day and month, the start date will be imputed as the first day of the year, while the end date will be imputed as the last day of the year

5.1.1.9. Baseline

Unless otherwise specified, baseline will be defined as the last non-missing measurement taken prior to the first dose of study drug (Advate or BIVV001).

5.1.1.10. Visit Windows

It is expected that all visits will occur according to the protocol schedule of assessments. All data will be tabulated per the evaluation visit as recorded on the electronic case report form (eCRF) even if the assessment is outside of the window for that study visit. Unscheduled visits will be included in data listings, but no assignment to a study visit will be made for the purpose of summary tabulations.

In the occurrence of repeat assessments within the same visit window, the last evaluation will be used for analysis.

5.1.2. Pooling Sites for Analysis

Data from all investigational sites will be pooled for the analysis, and no separate analysis by site will be performed.

5.1.3. Handling of Missing Data

No imputation due to missing data will be applied.

For the analysis datasets of AEs and concomitant medications/procedures, if the start/stop date of an AE/concomitant medication is missing or partial, the corresponding study day will be left blank. However, inferences will be made from the partial and missing dates to classify medications as prior and/or concomitant and AEs as treatment emergent or not treatment emergent. These inferences are described in Section 6.4 and Section 9.1, respectively.

5.2. Data Summaries

5.2.1. Continuous Variables

Continuous variables will be summarized using descriptive statistics including the number of non-missing values (n), mean, standard deviation (SD), median, minimum, and maximum. Where specified in the table shells, the 25th and 75th percentiles will also be provided.

Pharmacokinetic parameters will also be summarized using the geometric mean and percent coefficient of variation (%CV).

Means (arithmetic and geometric), medians, confidence intervals, and 25th and 75th percentiles will be presented to one decimal place beyond that with which the data was captured. Standard deviations will be presented to two decimal places beyond that with which the data was captured. Minimum and maximum will be displayed to the same number of decimal places as that with which the data was captured. %CV will be displayed to one decimal place for all PK parameters.

5.2.2. Categorical Variables

Categorical variables will be summarized by counts and percentages. All percentages will be rounded to one decimal place. The percentage will be suppressed when the count is zero. Unless otherwise specified, the denominator for all percentages will be the overall number of subjects (or other experimental unit, eg bleeding episodes) with non-missing data for a given summarization.

6. STUDY POPULATION

6.1. Disposition of Subjects

Subject disposition will be summarized for each dose level and overall using the All-Enrolled Analysis Set. The table will present the number and percentage of subjects in the Safety Analysis Set and the PK Analysis Set. In addition, the number of subjects who completed the study and the number of subjects who discontinued from the study early, including the primary reason for discontinuation, will be tabulated.

Subject disposition, including date of last visit and reason for early discontinuation, for subjects who did not complete the study, will be provided in a listing.

6.2. Demographic and Baseline Disease Characteristics

6.2.1. Demographics

Demographics will be summarized by dose level and overall using the Safety Analysis Set.

Demographic characteristics will include age, height, weight, and body mass index (BMI) at screening plus race, ethnicity, and country. Age will be summarized both as a continuous variable using descriptive statistics and categorically (<18, 18-24, 25-34, 35-44, 45-54, 55-64, ≥ 65 years). Height, weight, and BMI will be summarized using descriptive statistics where BMI is calculated as weight (kg) / height (m^2). Race, ethnicity, and country (United States, Japan) will be summarized categorically by number and percentage of subjects.

Demographics will also be presented in a listing using the All-Enrolled Analysis Set.

6.2.2. General Medical and Surgical History

Medical and surgical history will be recorded at screening. The number and percentage of subjects with any medical and surgical history will be summarized for each body system overall and by dose level using the Safety Analysis Set. A patient will be counted only once if the patient reported one or more occurrences of the same body system.

Medical and surgical history, including specific details, will also be presented in a listing using the All-Enrolled Analysis Set.

6.2.3. Hemophilia History

Hemophilia medical and bleeding history will be reported at screening and will be summarized by dose level and overall for the Safety Analysis Set.

Categorical summaries will be provided for lowest documented historical FVIII level (<1%, ≥1%), family inhibitor history, human immunodeficiency virus (HIV) status, Hepatitis C (HCV) status, Hepatitis B (HBV) status, blood type, [redacted], Rh factor, vaccination history, and types of FVIII product previously administered at study entry.

Time since diagnosis of hemophilia, number of bleeds in the past 3 months and typical dosing for treatment of bleeds (minor, moderate, major) will be summarized with descriptive statistics.

In addition, a summary of the most recent pre-study FVIII regimen and other prior FVIII regimens used in the past 3 months will be provided including categories for most recent pre-study FVIII regimen (prophylaxis, on-demand), time on pre-study regimen (>12 months, 6-12 months, < 6 months), and the frequency of injections for those subjects who indicated prophylaxis as their most recent pre-study regimen.

Hemophilia medical and bleeding history will also be presented in listings using the All-Enrolled Analysis Set.

6.3. Protocol Deviations

All protocol deviations will be recorded throughout the study. The overall number of subjects with major protocol deviations will be summarized by category using the Safety Analysis Set.

Protocol deviations will also be presented in listings using the All-Enrolled Analysis Set.

6.4. Non-study Drug Medications

6.4.1. Prior and Concomitant Medications

Prior medications include all medications taken within 30 days prior to the administration of the first dose of Advate.

A concomitant medication is any drug or substance administered from Day 1 of the study through the last study visit. Medications with missing start dates will be assumed to be concomitant, unless the stop date is before the Advate dosing date.

Data on both prior and concomitant medications will be summarized by dose level and overall for the Safety Analysis Set. In addition, prior and concomitant medications will also be presented in data listings for the All-Enrolled Analysis Set. In these listings, medications taken during a major surgical period will be flagged.

Number of days from study drug administration (both for Advate and BIVV001) to the start date of the medication will be included and calculated using the following formula:

If medication start date is on or after study drug administration, days from study drug administration = medication start date – study drug administration date + 1. If medication start date is before study drug administration, days from study drug administration = medication start date – study drug administration date.

Number of days from study drug administration to the stop date of prior or concomitant medication will be calculated similarly.

If start or stop dates are incomplete or missing, then the number of days from study drug administration to the start/stop date will be reported as missing – no imputation of dates will be performed.

6.4.2. Other Therapies and Procedures

Other therapies and procedures will be displayed in a data listing for the All-Enrolled Analysis Set. The listing will include therapy or procedure name, start date, end date, reason for therapy

or procedure and whether the procedure was considered surgical and the surgery category (minor/major).

6.5. Study Drug

Study drug administration for both Advate and BIVV001 will be listed using the Safety Analysis Set. This includes the study drug administered, lot number, nominal IU amount administered per vial, actual IU amount administered per vial, number of vials injected, total actual IU injected, total volume injected, and infusion start and stop dates and times.

6.6. 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. Bleeding episodes will be collected during the study including date and time of bleeding episodes, location of bleed, type of bleed, and treatment for bleed. If bleed is treated with FVIII infusion, the date and time of infusion will be collected.

Bleeding episodes will be presented by dose level and subject in a data listing.

7. EFFICACY ANALYSES

No efficacy analyses are planned for this study. 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.

8. PHARMACOKINETIC ANALYSES

All PK analyses will be performed based on the PK analysis set (PKAS). The detailed methodology and software used will be documented in the PK report.

8.1. Summary of FVIII Activity

For Advate (FVIII) treatment, FVIII activity (one-stage clotting and chromogenic assays) will be assessed at screening, just prior to the administration of Advate (pre- dose of 25 IU/kg or 65 IU/kg) at 0.5, 1, 6, 24, 48, and 72 hours post-injection.

For BIVV001 treatment, FVIII activity (one-stage clotting and chromogenic assays) will be assessed just prior to the administration of BIVV001 and at 0.17, 0.5, 1, 3, 6, 9, 24, 48, 72, 96, 120, 168, and 240 hours (10 days) post injection for subjects administered the low dose of BIVV001 and additionally at 288 and 336 hours (14 days) post injection for those subjects administered the high dose of BIVV001 and at the End of Study/Early Termination Visit.

Hours from treatment will be calculated as the time elapsed from initiation of the Advate injection to sample collection for the Screening period and Advate treatment period or as the time elapsed from initiation of the BIVV001 injection to sample collection for the BIVV001 treatment period.

FVIII activity will be summarized by study drug, dose level, visit, and by one-stage clotting assay and two-stage chromogenic assay, respectively and presented in one data listing for each study drug for the Safety Analysis Set. Summary descriptive statistics will include the number of non-missing values, mean, geometric mean, standard deviation, percent coefficient of variation, minimum, and maximum.

FVIII activity versus time profiles will be plotted in both original and log scale for each subject by study drug for both assays. In addition, the mean FVIII activity versus time profiles at each dose level will be constructed for the two study drugs in the original and log scale for both assays.

8.2. PK Parameter Analysis

All individual PK parameter calculations will be performed using actual time points calculated relative to the time of starting administration of Advate or BIVV001.

Individual PK parameter estimates will be listed for each subject and summarized descriptively by drug and dose level group for both FVIII activity assays. Summary descriptive statistics will include the number of observations, arithmetic and geometric means, standard deviation, coefficient of variation, 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.

9. SAFETY ANALYSES

All safety analyses will be conducted using the Safety Analysis Set.

9.1. Adverse Events

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes and Preferred Terms (Version 20.0 or later). Any AE experienced by the subject from the day of signing the Informed Consent Form until 28 days after BIVV001 administration will be recorded on the eCRF, regardless of the severity of the event or its relationship to study treatment.

A treatment-emergent AE (TEAE) is defined as any adverse event that begins on or after the study treatment (Advate or BIVV001) and within 28 days after BIVV001 administration. AEs with missing start dates will be assumed to be treatment-emergent, unless the stop date is before the dosing date. An AE starting on or after the single dose of study-administered Advate but before the single dose of study-administered BIVV001 will be counted in the Advate Treatment Period. An AE starting on or after the single administration of study-administered BIVV001 and up to the end of study will be counted in the BIVV001 Treatment Period. During the BIVV001 Treatment Period, subjects may resume treatment with their pre-study FVIII product after completing Visit 14 activities. Adverse events that occur during pre-study FVIII product use will be summarized in the BIVV Treatment Period summaries as well as in a separate summary. Adverse events that occur during a major surgical period will be listed separately and will not be included in the AE summary tables.

In general, AEs will be summarized by subject incidence by dose level and overall for the BIVV001 Treatment Period and separately for the Advate Treatment Period. In addition, all AEs will be presented in a data listing by dose level and subject. In this listing, AEs that occur prior to study treatment and AEs that occur during a major surgical period will be flagged.

9.1.1. Overall Summary of Treatment-Emergent Adverse Events

An overall summary of treatment-emergent adverse events (TEAEs) will be provided which tabulates the number and percentage of subjects who experience a TEAE, related TEAE, treatment-emergent SAE, related treatment-emergent SAE, and the number and percentage of subjects who withdrew from the study due to an AE. The overall summary will be provided by dose level for the BIVV001 Treatment Period and separately by dose level for the Advate Treatment Period.

9.1.2. Treatment-Emergent Adverse Events

The incidence of TEAEs will be presented by system organ class, preferred term, and dose level for the BIVV001 Treatment Period and separately for the Advate Treatment Period. In addition, the incidence of TEAEs will be presented by preferred term in descending order of incidence. In these summaries, adverse events that occur during pre-study FVIII product use will be summarized in the BIVV Treatment Period as well as in a separate summary. At each level of patient summarization, a patient is counted once if the patient reported one or more events. Percentages will be based on the number of patients at each dose level for the Safety Analysis Set.

9.1.3. Severity of Adverse Events

The severity of AEs will be recorded on the AE form as "Mild", "Moderate", or "Severe". A summary of TEAEs by system organ class, preferred term, dose level, and severity will be presented for the BIVV001 Treatment Period and separately for the Advate Treatment Period.

In addition, all severe adverse events will be presented in data listings by dose level and subject.

9.1.4. Relationship of Adverse Events to Study Drug

Treatment-emergent AEs will be classified by relationship to study drug as "Not Related", "Related to Advate", or "Related to BIVV001". A summary of related TEAEs by system organ class, preferred term, and dose level will be presented for the BIVV001 Treatment Period and separately for the Advate Treatment Period.

In addition, all related adverse events will be presented in data listings by dose level and subject.

9.1.5. Serious Adverse Events

Any AE reported as resulting in death, immediate risk of death (life threatening), inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or a congenital/anomaly/birth defect will be classified as serious adverse event (SAE). An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above.

A summary of treatment-emergent SAEs by system organ class, preferred term, and dose level will be presented for the BIVV001 Treatment Period and separately for the Advate Treatment Period.

In addition, all SAEs will be presented in data listings by dose level and subject.

9.1.6. Adverse Events Leading to Study Withdrawal

All AEs reported on the AE form with the question "Was the subject terminated from study due to this AE" answered "Yes" will be presented in data listings by dose level and subject.

9.1.7. Death

All patient deaths during the study will be recorded on the Death form and will be presented in data listings by dose level and subject.

9.2. Clinical Laboratory Evaluations

The following protocol required laboratory tests will be performed:

- Hematology: red blood cell count, white blood cell count and differential, platelet count, hemoglobin, and hematocrit
- Clinical chemistry: ALT; AST; alkaline phosphatase; gamma-glutamyl transferase; bilirubin; blood urea nitrogen; 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 FVIII activity, VWF ristocetin cofactor activity, and VWF antigen)
- [redacted]
- 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.

Refer to Section 5 of the protocol for the timing of assessments.

Laboratory assessments taken during the surgery period will be listed only and will not be included in the laboratory data summaries.

9.2.1. Hematology and Chemistry

Hematology and chemistry data and change from baseline will be summarized over time using descriptive statistics for each drug and dose level group using the Safety Analysis Set. The data will also be presented in a listing using the Safety Analysis Set. A flag for lab results outside the reported normal range will be included in the listing. In addition, lab results that occur during a major surgical period will be flagged.

9.2.2. Urinalysis

Urinalysis data will be presented in a listing using the Safety Analysis Set. A flag for lab results outside the reported normal range will be included in the listing. In addition, lab results that occur during a major surgical period will be flagged.

9.2.3. Coagulation Parameters

Samples for coagulation parameters (PT, aPTT, D-dimer, international normalized ratio, thrombin-anti-thrombin, and prothrombin fragment 1.2, and vWF) will be collected at Screening, Visits 2 and 3 (pre-injection for Advate and 1, 6, and 24 hours post-injection), Visits 6 and 7 (pre-injection for BIVV001 and 1, 6, and 24 hours post-injection), Visit 14 (14 days post-injection for BIVV001), and at the End of Study/Early Termination Visit.

Hours from treatment will be calculated as the time elapsed from initiation of the Advate injection to sample collection for the Screening period and Advate treatment period or as the time elapsed from initiation of the BIVV001 injection to sample collection for the BIVV001 treatment period.

Coagulation data and change from baseline will be summarized over time using descriptive statistics for each drug and dose level group using the Safety Analysis Set. The data will also be presented in a data listing using the Safety Analysis Set.

9.2.4. Inhibitor Development using the Nijmegen-modified Bethesda Assay

An inhibitor assessment using the Nijmegen-modified Bethesda assay will be performed for all subjects at Screening, Visit 2 (pre-injection for Advate), Visit 6 (pre-injection for BIVV001), Visit 14 (14 days post-injection for BIVV001) and the End of Study/Early Termination Visit.

The number and percentage of subjects who test positive for inhibitor will be presented for each drug by dose level. In addition, inhibitor status will be presented by dose level and subject in a listing using the Safety Analysis Set.

9.2.5. Anti-rFVIIIFc-VWF-XTEN Antibodies

The plasma samples for anti-rFVIIIFc-VWF-XTEN antibody will be collected at Screening, Visit 2 (pre-injection for Advate), Visit 6 (pre-injection for BIVV001), Visit 14 (14 days post-injection for BIVV001) and the End of Study/Early Termination Visit.

The number and percentage of subjects who test positive for anti-rFVIIIFc-VWF-XTEN antibodies will be presented by dose level. In addition, antibody status will be presented by dose level and subject in a listing using the Safety Analysis Set.

[redacted]

9.3. Physical Examination

Physical examination will be performed at Screening and the End of Study/Early Termination Visit. The physical exam will include the following: dermatological, HEENT, respiratory, cardiovascular, gastrointestinal, endocrine/metabolic, genitourinary, neurological/psychiatric, hematologic/lymphatic, musculoskeletal, allergies, general appearance, and other findings of note.

Physical examination results will be presented for abnormal findings by dose level and subject in a data listing using the All-Enrolled Analysis Set.

9.4. Vital Signs

Vital signs include blood pressure, pulse, respiratory rate, and oral temperature. Vital sign data and change from baseline will be summarized over time using descriptive statistics for each drug

and dose level using the Safety Analysis Set. The data will also be presented by dose level and subject in a data listing using the Safety Analysis Set.

10. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

Changes to the planned analyses from the final protocol are listed below.

Interim Analysis

The timing of the interim analysis was changed to allow for an earlier descriptive analysis after at least 3 subjects have completed the 28-day safety observation period and have available safety and PK data instead of including the entire low dose cohort. The interim analysis will be of a descriptive nature and no formal hypothesis testing will be performed.

Pharmacokinetic Analysis Set (PKAS)

The definition of the PKAS was clarified by the clinical pharmacologist as all subjects who have adequate blood sample collections (following Advate or BIVV001 administration) to assess key PK parameters, as determined by the PK scientist. The final protocol defined the PKAS 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.

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12. APPENDIX

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