STATISTICAL ANALYSIS PLAN

NCT Number: NCT02973087

Study Title: A PROSPECTIVE, PHASE 3, OPEN-LABEL, INTERNATIONAL MULTICENTER STUDY ON EFFICACY AND SAFETY OF PROPHYLAXIS WITH rVWF IN SEVERE VON WILLEBRAND DISEASE

Study Number: 071301

SAP Version and Date:

Version 3: 29 Sep 2020

STATISTICAL ANALYSIS PLAN

Recombinant von Willebrand factor (rVWF, vonicog alfa) (BAX 111)
PHASE 3

A PROSPECTIVE, PHASE 3, OPEN-LABEL, INTERNATIONAL MULTICENTER STUDY ON EFFICACY AND SAFETY OF PROPHYLAXIS WITH rVWF IN SEVERE VON WILLEBRAND DISEASE

PROTOCOL IDENTIFIER: 071301

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REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	2020 APR 02	Final
2.0	2020 AUG 02	Added supplemental analyses of Modified FAS (subjects with no data removed due to inadequate source documentation). Removed by-sponsor assessment of AE relationship to IP. Updated table of contents.
3.0	29 SEP 2020	Clarification that the primary efficacy endpoint will be based on the treated spontaneous bleeding episodes for both historical and on-study period, to align with Protocol Section 11.1. Clarifications, administrative changes and/or rewording included to improve the readability and clarity of the SAP.

TABLE OF CONTENTS

ABBREVIATIONS

Ab	antibodies
ABR	annualized bleeding rate
ADAMTS13	a murine disintegrin and metalloproteinase with a thrombospondin type 1 motif, number 13
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Class
AUC	area under the concentration versus time curve
$AUC_{0\text{-}96hr}$	area under the concentration versus time curve from 0 to 96 hours post-infusion
$AUC_{0\text{-}tau:ss}$	area under the concentration versus time curve from 0 to end of the partial dosing interval (at steady state)
$AUC_{0\text{-}tlast}$	area under the concentration versus time curve from 0 to the last measurable concentration
$AUC_{0\text{-}\infty}$	area under the concentration versus time curve from 0 extrapolated to infinity
BLQ	below the limit of quantification
BMI	body mass index
BUN	blood urea nitrogen
CBC	complete blood count
CD4	helper T cell
CHO	Chinese hamster ovary
CI	confidence interval
CL	apparent total body clearance
$C_{max:ss}$	maximum concentration during the partial dosing interval (at steady state)
C_{max}	maximum observed concentration
$C_{min:ss}$	minimum observed concentration (at steady state)
C_{min}	minimum observed concentration
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization
CTMS	clinical trial management system
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form

eDiary	electronic diary
EMA	European Medicines Agency
EOS	end of study
[redacted]	[redacted]
FAS	full analysis set
FVIII	Factor VIII
FVIII:C	Factor VIII clotting activity
GI	gastrointestinal
GLMM	generalized linear mixed model
GP	general practitioner
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	health resources
[redacted]	[redacted]
ICF	Informed Consent Form
IgG	immunoglobulin G
IgM	immunoglobulin M
INR	international normalized ratio
IP	investigational product
IR	incremental recovery
IU	international units
IV	intravenous
LDH	lactate dehydrogenase
LLOQ	lower limit of quantitation
LSM	least-square mean
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCS	mental component score (SF-36)
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRT	mean residence time
NTE	non-treatment emergent
OD	on-demand
OPE	observation period for efficacy
[redacted]	[redacted]
PD	pharmacodynamic
pdVWF	plasma-derived Von Willebrand Factor
PK	pharmacokinetic

PKAS	pharmacokinetic analysis set
PK/PD	pharmacokinetic/pharmacodynamic
PPAS	per-protocol analysis set
PRO	patient-reported outcome
PT	preferred term
Q1	25th percentile
Q3	75th percentile
RBC	red blood cells
rFVIII	recombinant Factor VIII
rVWF	recombinant von Willebrand factor
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SAS	Statistical Analysis System
SD	standard deviation
SDA	study drug administration diary
SDAD	study drug administration details
SE	standard error of the mean
[redacted]	[redacted]
SI	Système International
SMQ	Standardized MedDRA® Query
SOC	system organ class
STEAE	serious treatment-emergent adverse event
$t_{1/2}$	apparent terminal half-life
TEAE	treatment emergent adverse event
$t_{max:ss}$	minimum time to reach C_{max} (at steady state)
t_{max}	minimum time to reach C_{max}
VAS	visual analogue scale
V_{ss}	apparent volume of distribution at steady state
VWD	von Willebrand disease
VWF	von Willebrand factor
VWF:Ac	von Willebrand factor activity
VWF:Ag	von Willebrand factor antigen
VWF:CB	von Willebrand factor collagen binding activity
VWF:RCo	von Willebrand factor: ristocetin cofactor
[redacted]	[redacted]
WBC	white blood cells
WHO	World Health Organization
WHO-DD	World Health Organization - Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy, safety, pharmacokinetic/pharmacodynamic (PK/PD) and [redacted] data, as described in the final Study Protocol Amendment 6 dated 12 MAR 2018. Specifications for tables, figures and listings are contained in a separate document.

The purpose of this phase 3 study is to investigate the efficacy, safety (including immunogenicity, thrombogenicity and hypersensitivity reactions), pharmacokinetics (PK), [redacted] and [redacted] of prophylactic treatment with recombinant Von Willebrand Factor (rVWF, vonicog alfa) in adult subjects with severe Von Willebrand disease (VWD).

2. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

The primary objective of this study is to prospectively evaluate the annualized bleeding rate (ABR) for spontaneous bleeding episodes while on prophylactic treatment with rVWF (vonicog alfa) and to compare it to the subject's historical ABR for spontaneous bleeding episodes.

*The annualized bleeding rate (ABR) will be assessed based upon each individual spontaneous bleed, requiring coagulation factor replacement therapy, i.e., rVWF (vonicog alfa) treatment.(Protocol section 11.1). Hereafter these bleeding episodes (BEs) will be referred to as "**treated BEs**"*

2.1.2 Secondary Objectives

Secondary objectives are to assess:

- Additional efficacy of prophylactic treatment with rVWF (vonicog alfa)
- Safety of rVWF (vonicog alfa), including immunogenicity, thrombogenicity and hypersensitivity
- Pharmacokinetics (PK) of rVWF (vonicog alfa) and pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in Factor VIII (FVIII) activity

2.1.3 Exploratory Objectives

[redacted]

2.2 Endpoints

2.2.1 Primary Outcome Measure

2.2.1.1 Efficacy of Prophylactic Treatment with rVWF

- The primary outcome measure is ABR for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa).

2.2.2 Secondary Outcome Measures

2.2.2.1 Additional Efficacy of Prophylactic Treatment with rVWF

- ABR percent reduction success for OD subjects, defined as at least 25% reduction of ABR based on spontaneous BEs during rVWF (vonicog alfa) prophylaxis relative to the subject's own historical ABR during on-demand treatment prior to this study.

- ABR preservation success for pdVWF switch subjects, defined as achieving an ABR based on spontaneous BEs during rVWF (vonicog alfa) prophylaxis that is no greater than the subject's own historical ABR based on spontaneous BEs during prophylactic treatment with pdVWF prior to this study.

- Categorized spontaneous ABR defined as 0, >0 through 2, >2 through 5, >5 during prophylactic treatment with rVWF (vonicog alfa)

- Total number of infusions and the average number of infusions per week during prophylactic treatment with rVWF (vonicog alfa)

- Total weight adjusted consumption of rVWF (vonicog alfa) during prophylactic treatment

- ABR for spontaneous bleeding episodes by location of bleeding (GI, epistaxis, joint bleeding, menorrhagia, oral and other mucosa, muscle and soft tissue, etc.) while on prophylactic treatment with rVWF (vonicog alfa)

-

2.2.2.2 Safety

- Adverse events (AEs): incidence, severity, causality

- Occurrence of thromboembolic events

- Occurrence of hypersensitivity reactions

- Development of neutralizing antibodies to VWF and FVIII

- Development of total binding antibodies to VWF and FVIII

- Development of binding antibodies to Chinese hamster ovary (CHO) proteins, mouse immunoglobulin G (IgG) and rFurin

- Clinically significant changes in vital signs and clinical laboratory parameters relative to baseline

2.2.2.3 Pharmacokinetics (PK) and Pharmacodynamics (PD)

- PK parameters after a washout for OD subjects: incremental recovery (IR), terminal half-life ($T_{1/2}$), mean residence time (MRT), area under the concentration versus time curve from 0 to infinity ($AUC_{0-\infty}$), area under the concentration versus time curve from 0 to the last measurable concentration ($AUC_{0-tlast}$), maximum plasma concentration (C_{max}), minimum time to reach the maximum concentration (T_{max}), volume of distribution at steady state (V_{ss}) and clearance (CL) based on von Willebrand Factor Ristocetin Cofactor (VWF:RCo) activity, von Willebrand Factor Antigen (VWF:Ag), von Willebrand Factor Collagen Binding (VWF:CB) activity

- PD parameters after a washout for OD subjects: C_{max}, T_{max}, and $AUC_{0\text{-}tlast}$ as measured in Factor VIII (FVIII) activity by the 1-stage clotting assay (FVIII:C)

- PK parameters at steady state for OD and switch subjects: area under the concentration versus time curve from 0 to end of the partial dosing interval ($AUC_{0\text{-}tau;ss}$), maximum concentration during the partial dosing interval ($C_{max;ss}$), minimum time to reach the maximum concentration ($T_{max;ss}$) and minimum concentration during the partial dosing interval ($C_{min;ss}$) based on VWF:RCo, VWF:Ag and VWF:CB

- PD parameters at steady state for OD and switch subjects: $AUC_{0\text{-}tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$ as measured in FVIII activity by the 1-stage clotting assay

- Time course of FVIII clotting activity (FVIII:C) levels

2.2.3 Exploratory Outcome Measures

2.2.3.1 [redacted]

[redacted]

2.2.3.2 [redacted]

[redacted]

[redacted]

2.2.3.3 [redacted]

[redacted]

2.2.3.4 [redacted]

[redacted]

2.3 Estimands

This is a single-arm study with no planned statistical testing and therefore no Type I error control. The primary and 2 secondary estimands deemed most likely to support regulatory decisions are described in Table 1.

Table 1. Estimands

Estimand	Definition	Attributes			
		A: Population	**B: Variable or endpoint**	**C: Strategy for addressing intercurrent event**	**D: Population-level summary**
Primary	The primary estimand is the annualized bleeding rate (ABR) for treated spontaneous bleeding episodes during prophylactic treatment with rVWF (vonicog alfa) in a Full Analysis Set (FAS) of adult subjects with severe VWD	Study subjects identified per inclusion and exclusion criteria as stated in the protocol who receive prophylactic treatment (FAS)	ABR is calculated as the number of treated spontaneous bleeding episodes (BE) divided by the number of days on prophylactic treatment with rVWF, in years (i.e. [number of BEs/number of days] / by 365.2425).	The duration of the on-treatment observation period may vary due to early discontinuation. The variation will be addressed by annualization of the bleeding rate.	The ratio of the prospective to historic annualized rate of treated spontaneous bleeding episodes will be calculated based on a negative binomial regression using bleeding episodes from the first 12 months of prophylactic treatment. A 95% confidence interval will be provided using the model based standard error estimate. “On-demand” and “switch” subjects will be analyzed separately.

Estimand	Definition	Attributes			
		A: Population	**B: Variable or endpoint**	**C: Strategy for addressing intercurrent event**	**D: Population-level summary**
Secondary	ABR percent reduction success achieved by OD subjects	Study subjects identified per inclusion and exclusion criteria as stated in the protocol who receive prophylactic treatment (FAS)	ABR percent reduction success, defined as at least 25% reduction of the ABR for treated spontaneous BEs during rVWF (vonicog alfa) prophylaxis relative to the subject's own historical treated spontaneous ABR	The duration of the on-treatment observation period may vary due to early discontinuation. The variation will be addressed by annualization of the bleeding rate.	Number and percentage of OD subjects who achieve at least 25% reduction in ABR for treated spontaneous BEs during the first 12 months of prophylactic treatment with rVWF, compared to the historical period. A Clopper-Pearson CI for the percentage of subjects who achieve success will be provided.

Estimand	Definition	Attributes			
		A: Population	B: Variable or endpoint	C: Strategy for addressing intercurrent event	D: Population-level summary
Secondary	ABR preservation success in switch subjects, defined as achieving a ABR for treated spontaneous BEs during 12 months of rVWF (vonicog alfa) prophylaxis that is no greater than the subject's own historical ABR for treated spontaneous BEs during prophylactic treatment with pdVWF	Switch subjects who receive prophylactic treatment with rVWF (vonicog alfa)	Preservation success, defined as achieving an ABR for spontaneous bleeding episodes during rVWF (vonicog alfa) prophylaxis that is no greater than the subject's own historical ABR for spontaneous BEs during prophylactic treatment with pdVWF	The duration of the on-treatment observation period may vary due to early discontinuation. The variation will be addressed by annualization of the bleeding rate.	Number and percentage of switch subjects whose ABR for treated spontaneous BEs during the first 12 months of prophylactic treatment with rVWF is not greater than their historical ABR. A Clopper-Pearson CI for the percentage of subjects who achieve success will be provided.

3. STUDY DESIGN

3.1 General Description

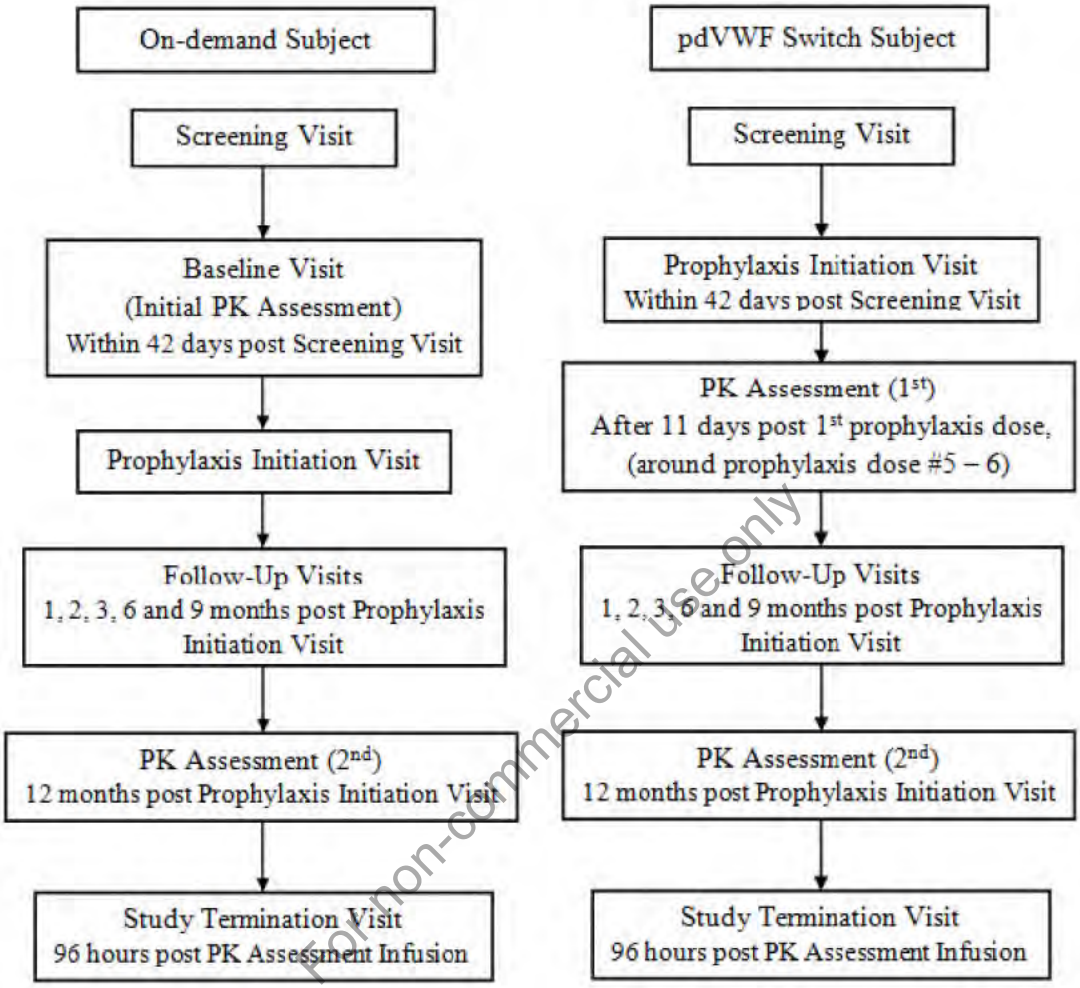
This is a phase 3, prospective, open-label, uncontrolled, non-randomized, international multicenter study evaluating efficacy, safety, including immunogenicity, thrombogenicity and hypersensitivity reactions, as well as PK/PD, [redacted] and [redacted] of prophylactic treatment regimen with rVWF (vonicog alfa) in adult subjects with severe VWD.

Subjects transitioning from on-demand treatment (OD subjects) or subjects switching from prophylactic treatment with pdVWF (switch subjects) will receive prophylactic treatment with rVWF (vonicog alfa) for a 12-month period (maybe longer, up to 15 months, for certain subjects). The starting dose will be 50 ± 10 IU/kg rVWF twice weekly for the OD subjects or will be based on their prior pdVWF dose for the switch subjects. The dose may be further individualized based on the PK data, subject's history of bleeding episodes, and the results from clinical and laboratory assessments (see Protocol Section 8.6.4.3).

The subject participation period will be approximately 15 - 18 months from enrollment to completion (i.e., last study visit), unless the subject is prematurely discontinued. The overall duration of prophylactic treatment with rVWF per subject will be 12 – to 15 months (Study treatment period can be extended by up to 3 months to accommodate participation in the continuation study for the qualified subjects and will be exercised only if the continuation study start up is delayed beyond the completion of subject's 12-month visit.). During this period any bleeding episodes requiring substitution therapy with VWF concentrate to control bleeding will be treated with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa). The dose will be according to the bleeding type and severity and it will be adjusted to the clinical response (see Protocol Section 8.6.4.4.2).

Protocol Figure 1, reproduced below, summarizes the overall study design. Details of the scheduled study procedures and assessments for each subject group are presented in Protocol Section 20.2 and Protocol Section 20.3.

Figure 1. Study Design for Baxalta Clinical Study 071301



3.2 Randomization

This is a non-randomized open-label, active-treatment clinical study.

3.3 Blinding

Not applicable.

3.4 Sample Size and Power Considerations

Approximately 22 adult subjects with severe VWD (baseline VWF:RCo <20 IU/dL) will be included in the study. The aim is to have at least 8 subjects in each subject group (OD and switch). A total of at least 5 type 3 VWD subjects will be followed for 12 months.

Sample size is not based on a power calculation for a significance test. No formal statistical tests are planned in the study. The sample size is driven by practical considerations (primarily the enrollment of a rare patient population) and EMA Guideline on the Clinical Investigation of Human Plasma Derived von Willebrand Factor Products (CPMP/BPWG/220/02).

3.5 Stopping Rules

This study will be stopped if 1 or more of the following criteria are met in the absence of any other possible and medically plausible causal attribution (e.g., underlying or concurrent condition, use of concomitant medication, subject's medical history, etc.):

1. Two subjects develop a life-threatening or fatal thromboembolic event

2. Two subjects develop life-threatening or fatal severe hypersensitivity reactions (e.g., anaphylaxis)

3. Any subject develops acute hepatic failure

4. Two subjects develop rVWF neutralizing antibodies that are considered clinically significant by the investigators and are associated with significant decrease of efficacy or serious adverse reactions.

The study may be stopped at any time by the sponsor. Ultimately, the sponsor will decide whether to terminate, temporarily halt or modify the study based on the data monitoring committee (DMC)'s review and recommendation on all relevant cases, including those that meet the stopping criteria listed above.

4. STATISTICAL ANALYSIS SETS

4.1 All Subjects Enrolled Set

The All Subjects Enrolled Set will consist of all subjects who have signed an Informed Consent Form (ICF).

4.2 Safety Analysis Set

The Safety Analysis Set (SAF) will consist of all subjects in the Enrolled Set who received any amount of IP (rVWF, vonicog alfa), as documented in the investigational product (IP) administration electronic diary (eDiary), *Study Drug Administration* eCRF, *Study Drug Administration Details* eCRF or *Pharmacokinetic Infusion* eCRF.

4.3 Full Analysis Set

The Full Analysis Set (FAS) will be composed of all subjects who receive prophylaxis IP treatment (primary analysis population).

4.4 Modified Full Analysis Set

The Modified Full Analysis Set (MFAS) will be composed of all subjects who received prophylaxis treatment with IP and did not have data identified to be removed due to lack of proper ALCOAC source documentation. This analysis set will be used as supportive analysis of efficacy.

4.5 Per-Protocol Analysis Set

The Per-Protocol Analysis Set (PPAS) will consist of subjects in the FAS who are ≥70% compliant regarding the number of scheduled prophylactic infusions (i.e., <30% of planned infusions of IP are missed within the visit interval of 3 months). This will be measured by the ratio of actual number of infusions to planned number of infusions; see Section 5.8 for details of the derivation.

Subjects who met all study entry criteria (ie, met **all inclusion** and **no exclusion** criteria) and who had no major protocol violations that might impact primary efficacy assessments will be included in the PPAS.

Major protocol deviations which are expected to lead to exclusion from the PPAS are as follows:

1. Any violation of inclusion and/or exclusion criteria (i.e., ineligible subjects, regardless of treatment status)

2. Compliance with study medication

    - Subjects who receive less than 70% of planned infusions during the time in study will be excluded from the PPAS

3. Incorrect timing of assessments

    - Not applicable. Efficacy endpoints are event-based rather than scheduled.

4. Prohibited concomitant medications

   The use of any of the following during the study will result in subject exclusion from the PPAS:

   - Non-topical immunomodulating drugs other than anti-retroviral chemotherapy (e.g., α-interferon, or corticosteroid agents at a dose equivalent to hydrocortisone greater than 10 mg/day), if used for more than 3 months during the study

   - Any other IP or investigational device from another clinical trial (except rVWF and FVIII administered under the surgery protocol)

   - Repeated use of other VWF products for prophylaxis or for the treatment of bleeding episodes during the study

Prior to conducting any analysis of the PPAS, a protocol deviations review meeting of IQVIA CTMS data will be held to determine final subject exclusions. At a minimum, the meeting will be attended by representatives of Biostatistics, Data Management and Clinical Development (including medical monitors/advisors) teams from both IQVIA and the Sponsor. Precise reasons for excluding subjects from the PPAS will be documented and approved in writing by the Sponsor prior to database lock.

4.6 Pharmacokinetic and Pharmacodynamic Analysis Sets

4.6.1 Pharmacokinetic and Pharmacodynamic (PK) Full Analysis Set

The PK Full Analysis Set (PKFAS) will be composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post-dose measurement for pharmacokinetic and/or pharmacodynamic analysis.

4.6.2 Pharmacokinetic and Pharmacodynamic (PK) Per Protocol Analysis Set

The PK Per Protocol Analysis Set (PKPPAS) is defined as a subset of the PKFAS. Subjects who met the following additional criteria will be included in the PKPPAS: Had no major violation of the protocol which affected the PK period of the study; see Section 5.9.

PK/PD samples with unknown dosing time, unknown actual or planned collection date/time, or where the concentration could not be determined, or where the results were

biologically implausible, will be excluded from the Pharmacokinetic/Pharmacodynamic analysis and the reasons for exclusion will be documented.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

A listing of the All Subjects Enrolled Set (i.e., the Enrolled Set) will present disposition in current study, the date and time of informed consent, any inclusion/exclusion criteria not met, any prior protocol participation (if known and available), and the subject group (OD or switch). A separate listing of Screen Failures will be presented along with reasons for screen failure and details of any AEs.

A listing of the Enrolled Set will display inclusion and exclusion status from each defined analysis set, including the reason(s) for exclusion where applicable.

A summary of disposition and analysis sets will be presented in a table on the Enrolled set. The number and percentage of subjects who completed and prematurely discontinued from the study will be presented for each subject group and overall. Reasons for premature discontinuation from the study as recorded on the *Completion/Termination* page of the eCRF will be summarized (number and percentage) by subject group and overall. Subjects who prematurely discontinued from the study will be listed by discontinuation reason.

In addition, the duration of the enrollment period, in days, will be summarized by study site and overall. Duration of enrollment will be calculated as (last date of contact for the last subject at that site - the first date of informed consent for the first subject at that site + 1).

5.2 Demographic and Other Baseline Characteristics

Descriptive summaries of demographic and selected baseline characteristics will be presented by subject group and overall for the SAF, FAS (if different from the SAF), MFAS and PPAS. Demographic and screening characteristics will be listed for the SAF.

The following demographic characteristics from the *Demography* eCRF will be summarized in a table:

- Age (years)
- Sex
- Child-bearing potential
- Ethnicity
- Race

Additional baseline characteristics will be summarized in separate tables, as outlined below. (Note: The expected data sources are shown in italics).

- Height (cm), weight (kg) and BMI (kg/m^2) *[Vital Signs eCRF and calculated BMI (derivation follows below)]*
- Von Willebrand disease subtype *[Von Willebrand Disease eCRF]*
- VWF:RCo, VWF:Ag, VWF:CB, FVIII:C, VWF:Ac Innovance *[Central lab data from Q2 external file]*
- Hepatitis A antibody, total hepatitis A antibody; hepatitis B surface antibody; hepatitis B core Ab; total hepatitis B surface antigen; hepatitis C virus antibody; parvovirus B-19; human immunodeficiency virus (HIV) (positive result) *[Central lab data from Q2 external file]*
- Human immunodeficiency virus (HIV) (positive result) and absolute Helper T cell (CD4) count < 200/mm^3 *[Inclusion/Exclusion Criteria eCRF]*
- Platelets *[Central lab data from Q2 external file]*
- International normalized ratio (INR), activated partial thromboplastin time (aPTT), prothrombin time *[Central lab data from Q2 external file]*
- Pregnancy test results *[Pregnancy Test eCRF]*

- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, creatinine *[Central Lab data]*

Body mass index will be derived (accurately to 1 decimal place) from the eCRF height and weight as follows for presentation in summaries and listings:

BMI (kg/m^2) = weight (kg) / (height $(m)^2$).

Results obtained from the *Genetic Testing and Genetic Testing History* eCRFs will be listed. No summary is planned. These will include:

- Blood group and rhesus factor
- Human leukocyte antigen (HLA) genotype
- VWD gene mutation
- VWF multimer pattern
- Presence of a murine disintegrin and metalloproteinase with a thrombospondin type 1 motif, number 13 (ADAMTS13) activity (Yes/No) and measured levels in percentage

Urinalysis and other laboratory tests which were planned for the screening visit only and which might have unscheduled post-baseline assessments if clinically indicated will be presented with the clinical laboratory data (Section 7.2).

5.3 Medical and Surgical History

Medical and surgical history will be collected at the Screening Visit (Visit 1) on a *Medical History eCRF* and will be coded to a system organ class (SOC) and preferred term (PT) using the version of the Medical Dictionary for Regulatory Activities (MedDRA) which is specified in the data management coding guidelines. Medical history of any subject who transitions from a prior surgery rVWF (vonicog alfa) study will be used from the eCRF of the surgery protocol and copied into the eCRF of this prophylaxis study.

The subject's medical history will be described for the following body systems, including severity or surgery and start and end dates if known: eyes, ears, nose, and throat;

respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological and genitourinary.

These data will be summarized for subjects in the SAF for each subject group and overall. Listings will be provided using the SAF.

5.4 Prior/Concomitant Medications and Non-Drug Therapies

Prior medications and non-drug therapies are defined as any medication or non-drug therapy which has an end date prior to the date of the first dose of IP.

All medications and non-drug therapies used in the 2 weeks prior to study entry will be recorded on the *Concomitant Medication/Non-Drug Therapy eCRFs*. The medications and non-drug therapies of any subject who transitions from a prior surgery rVWF (vonicog alfa) study will be copied from the eCRF of the surgery protocol to the eCRF of this prophylaxis study.

Prior medications and non-drug therapies will be coded to a preferred term (PT) using the World Health Organization (WHO) Drug Dictionary Global. The dictionary will be updated periodically. The prior medication usage and prior non-drug therapies will be summarized by the number and percentage of subjects who used each medication or therapy, by PT, for each subject group and overall in the SAF. Multiple medication/therapy usage by a subject in the same category will be counted only once.

Missing or partial dates will be imputed as described in Section 12.7.2 prior to determining whether a medication or non-drug therapy is prior or concomitant.

Concomitant medications and non-drug therapies are defined as any medication or non-drug therapy which has a start date prior to the date of the first dose of IP and which continues after the first dose of IP, or which has a start date between the dates of the first and last doses of IP, inclusive. Any medication or non-drug therapy with a start date after the date of completion/discontinuation from study will not be considered concomitant.

Concomitant medications and non-drug therapies are recorded on the *Concomitant Medication/Non-Drug Therapy eCRFs* and coded using the same dictionary as prior medications. Concomitant medication/non-drug therapy usage will be summarized by the number and percentage of subjects receiving each medication by PT, for each subject group and overall, in the SAF. Multiple medication usage by a subject in the same category will be counted only once.

Missing or partial dates will be imputed as described in Section 12.7.2 prior to determining whether a medication or non-drug therapy is prior or concomitant. All prior and concomitant medications and non-drug therapies will be listed for the SAF.

5.5 Prior/Concomitant Procedures

A prior procedure is defined as a procedure that is performed prior to the first administration of IP. A concomitant procedure is defined as any procedure with a start date between the dates of the first and last doses of IP, inclusive. Missing or partial dates will be imputed as described in Section 12.7.2 prior to determining whether a procedure is prior or concomitant.

Prior and concomitant procedures are collected on the *Concomitant Medication/Non-Drug Therapy eCRFs.* Prior and concomitant procedures will be listed as reported for the SAF; coding is not expected.

Planned surgery will be summarized in a separate table. The number and percentage of subjects who planned surgery will be reported, along with the number of planned surgeries and a breakdown of the planned procedures by procedure classification, procedure category, anatomical site, anatomical location, and laterality.

5.6 Von Willebrand Treatment and Bleed History

The subject's medical history will include documented history of on-demand or pdVWF prophylaxis treatment for at least the past 12 months and documented history (e.g., patient charts and prescription information) of all bleeding episodes within the past 12 months (up to 24 months if available). The data will be recorded on a *Von Willebrand Treatment and Bleed History eCRF*.

Variables related to the history of bleeding episodes will include the number of months of history, number of unique bleeds, the historical ABRs for overall and treated spontaneous bleeding episodes as collected for up to 12 months prior to the study start (ie, prior to the first dose of study drug), the anatomical bleed site, cause, and severity.

Bleeding history will be summarized using descriptive statistics by subject group and overall. Bleeding history and history of prophylactic treatment will be listed for the SAF.

5.7 Exposure to IP

Infusions were to be recorded in the subject e-diary. Ultimately, some infusions were recorded on a paper diary or via site documentation of a phone call with the subject rather

than in the e-diary. The e-diary, paper diary, and other written documentation is all recognized as source documentation for infusions, although the quality of the documentation is known to vary. The infusion data recorded in the eCRF without source document verification was to be queried for removal from the study database.

The established processes for controlling and documenting changes to source documentation were applied; additionally, the e-diary has an audit trail for any required changes. The data from different sources are reconciled by study Data Management and clinical monitoring team prior to database lock.

Protocol Section 8.6.4 offers a complete description of the treatment to be administered and the conditions for adjusting subject weekly dose or dosing schedule. A summary is offered here for convenience, as rationale for the planned analysis of exposure to IP.

For OD subjects, the standard prophylactic dose is 50 ± 10 IU/kg rVWF:RCo, which may be increased up to 80 IU/kg in consultation with the Sponsor. All OD subjects will initially receive rVWF (vonicog alfa) twice per week (Protocol Table 1, Schedule A).

For pdVWF switch subjects, the weekly dose (IU/kg) of IP for each subject will be equivalent (± 10%) to the weekly VWF dose received during prophylactic treatment with pdVWF. The weekly dose of IP should be divided into 2 infusions (Protocol Table 1, Schedule A), with a maximum of 80 IU/kg/infusion. If needed, based on the total weekly dose or other clinical judgements, the weekly dose may be given as three infusions (Protocol Table 1, Schedule B). A once weekly dose regimen will be allowed after switch to rVWF (vonicog alfa) only if the subject has been on a once weekly dose regimen with pdVWF prior to this study.

In the event of an acute bleeding episode, the investigator will hold the subject's dosing schedule steady and increase the dose as needed (up to the maximum dose per infusion). If this does not suffice to reach a therapeutic dose to control the bleeding, then the weekly frequency of treatment may be increased. After bleed resolution, the treating physician may adjust the subject's prophylactic dose upward or downward. The schedule may also be adjusted to keep each infusion within the allowed dosing range.

In cases where a subject's endogenous Factor VIII level is low (i.e., below 30-40%) or is unknown and cannot be estimated from the subject's PK study, ADVATE (rFVIII, octocog alfa) may be administered with rVWF (vonicog alfa). Co-administration of rVWF and ADVATE may be done at any time it is clinically indicated.

5.7.1 Planned Analyses

Exposure to study drug will be reported by subject group and for the pooled groups, for rVWF alone, rVWF with ADVATE, and all rVWF (with or without ADVATE). The following quantities will be reported.

- Duration of treatment
  - The total number of subject-months of prophylactic study drug exposure in the study.
  - Reverse-cumulative duration in study, specifying how many subjects were observed for ≥1 month, ≥3 months, ≥6 months, ≥9 months, and ≥12 months
  - Reverse-cumulative duration of prophylactic treatment, specifying how many subjects were treated for ≥1 month, ≥3 months, ≥6 months, ≥9 months, and ≥12 months of prophylaxis
  - The total number of months of exposure to study drug per subject
  - The total number of months of prophylactic exposure to study drug, per subject

- Number of infusions
  - The total number of infusions administered during the study
  - The number and percentage of all infusions administered, by reason for infusion (prophylaxis, bleeding episode, maintain hemostasis, surgery)
  - The total number of infusions per subject administered during the study
  - The total number of prophylactic infusions per subject administered during the study

- Amount of rVWF (IU) used during the study
  - Total amount of study drug (IU) administered to subjects during the study, overall and by reason for treatment
  - The total weight-adjusted consumption of rVWF (IU/kg) per subject per month during the study
  - The total weight-adjusted prophylactic dose of rVWF (IU/kg) per month per subject

- Exposure to rVWF to treat bleeding events
    - Total number of bleeds treated
    - The number of infusions administered per subject per treated bleeding event, by type of bleeding event (spontaneous, traumatic, other)
    - The total dose of rVWF in IU/kg per subject per treated bleeding episode, by type of bleeding episode (spontaneous, traumatic, other)
    - The total dose of rVWF in IU/kg per subject per treated spontaneous bleeding episode, by severity of bleeding episode (based on the investigator's assessment of severity at resolution)

The summaries will be created for the SAF, FAS (if different from the SAF), MFAS, and PPAS. Also, a listing will be created for the SAF, by subject number and visit, giving the date and time of dose administration.

5.7.2 Related Definitions and Derivations

5.7.2.1 Study Observation Period

The on-study observation period is defined to begin on the day of first administration of study drug and to continue through the date of completion/discontinuation from study.

5.7.2.2 Overall Duration in Study

The overall duration in study will be calculated as (date of completion/termination – date of first dose + 1).

5.7.2.3 Treatment Duration by Reason for Treatment

For each subject, each day from the date of first dose to the date of completion/ termination (inclusive) will be classified into a unique treatment interval.

The first treatment interval will begin on the day of first infusion of study drug and will continue until the day prior to the next administration of study drug. Thereafter, a new treatment interval will start with each administration of study drug and will continue until the day before the next administration of study drug.

The days in each treatment interval will be assigned a reason for treatment, based on the collected reason for the infusion (prophylaxis, treatment of bleeding episode, surgery-related, etc.). If the reason for an infusion is missing at the time of final database lock, the infusion will be imputed as a prophylactic infusion. If an infusion is missing, the days from the target date of administration to the next actual administration will be classified

as lacking prophylactic coverage. The date of termination/completion will always be counted in the last treatment interval.

After a subject's days in study have been classified with respect to a reason for treatment (or as lacking coverage), then the subject's total number of days in the study will be summed by reason for treatment. Conversion from days to other units of time (weeks, months, or years) will be made to support analyses as needed, using the following formulae:

- Duration in weeks = duration (days) / 7
- Duration in months = 12 x duration (days) /365.2425
- Duration in years = duration (days) /365.2425.

The individual subject durations will be rounded to a scientifically meaningful level of precision after the time unit conversion and before summarization; specifically, the duration will be rounded to the closest whole week, 1/10 of a month, or 1/100 of a year.

5.7.2.4 Total Number of Infusions Per Subject

For each subject, the total number of infusions will be counted as the total number of unique infusions of rVWF which are administered between the dates of informed consent and termination from the study, inclusive, regardless of the date and time of administration. Any infusion which is begun will be counted. The reason for each unique infusion will be obtained from the *Study Drug Administration Details* eCRF and from the eDiary.

5.7.2.5 Total Dose (IU/kg) Per Subject

For each subject, the body weight-adjusted dose (IU/kg) will be derived as the number of units of rVWF infused (IU) divided by the last available body weight (kg) prior to the infusion. Refer to Section 12.7, Handling of Missing, Unused, and Spurious Data, for imputation schemes to be implemented.

The total dose (IU/kg) per subject will be determined as the sum of all doses, overall and by reason for infusion, during the study observation period in the current study.

5.7.2.6 Average Dose Per Subject Per Bleeding Event

Average dose per subject per bleeding event is defined as the sum of all doses (IU/kg or IU as applicable) given to treat bleeding episodes, divided by the number of unique bleeds recorded for the subject during the study observation period.

5.8 Treatment Compliance

The topic of treatment compliance applies only to the prophylactic treatment periods. Treatment compliance will be summarized for the SAF, FAS (if different from the SAF), MFAS, and PPAS.

5.8.1 Planned Analyses

5.8.1.1 Percent Compliance by Subject

The primary measure of treatment compliance will be the ratio of actual number of prophylactic infusions started to the planned number of prophylactic infusions in a specified time interval, expressed as a percentage (i.e., 100 x number of actual infusions/number of planned infusions). An infusion will be counted as having occurred if the infusion is started, even if it is interrupted or the whole dose is not administered for any reason.

The numbers of actual and planned doses for a subject may be obtained programmatically in several ways; one method is described here:

- Identify the start and stop dates of each prophylactic treatment interval in which there were no changes of the subject's assigned prophylactic dosing frequency; each day during the treatment period will fall in exactly 1 interval. (Note: If a change in the prophylactic dosing frequency occurred in a treatment interval, then break it into one or more shorter intervals, during which no changes in dosing frequency occurred.)
- Break the intervals to start/stop at 3, 6, 9, 12 months and end of study, as needed
- Calculate the number of weeks of prophylaxis in each interval as (interval end date – interval start date + 1) / 7, rounded to 1 decimal.
- Count the number of unique infusions administered in each interval, for which the reason for infusion was given as "prophylaxis"; then sum the counts across all intervals within each of the 3-month periods (i.e., 3, 6, 9, 12 months and end of study).

- Calculate the number of planned doses in each interval, based on the assigned dosing frequency, as (interval duration in weeks x number of planned doses per week)
- Sum the number of planned prophylactic doses across all treatment intervals within each 3-month period and round the sum to the closest integer.
- Calculate percent compliance for each 3-month period and overall as 100 x number of administered prophylactic doses / number of planned prophylactic doses.

Note: The total number of missed prophylactic doses plus administered prophylactic doses (either on or off schedule, whether completed or not) is expected to equal the number of planned prophylactic doses.

The following statistics will be provided by subject group and overall:

- Descriptive statistics for the per-subject percent treatment compliance (based on started infusions) during the study

- The number and percentage of subjects who were administered ≥70% of their scheduled infusions will be tabulated for each 3-month period and overall.

5.8.1.2 Percent of Prophylactic Infusions Within Recommended Dose Range

If possible, each prophylactic infusion will be classified as shown below:

	Protocol-specified Dose Range	
Category	On Demand Subjects	pdVWF Switch Subjects
Lower than recommended	<40 IU/kg	<90% of pre-switch dose of pdVWF
Within recommended range	40 to 80 IU/kg	90% of pre-switch dose to 80 IU/kg
Higher than recommended	>80 IU/kg	>80 IU/kg

The following statistics will be reported:

- The number and percentage of prophylactic infusions which were lower than, within, or higher than the recommended prophylactic dose range

- The number and percentage of subjects with 90% of prophylactic infusions at or above the minimum required prophylactic dose of 40 IU/kg
- The number and percentage of subjects with 90% of prophylactic infusions at or below the maximum allowed prophylactic dose (i.e. upper limit of allowed dose range) of 80 IU/kg/infusion
- The number and percentage of subjects with 90% of prophylactic infusions within the recommended prophylactic dose range of 40 IU/kg to 80 IU/kg/infusion
- Descriptive statistics for the per-subject percentage of completed infusions

5.8.1.3 Adherence to Planned Dosing Schedule

Adherence to the protocol-specified schedule of infusions will be evaluated using the following statistics:

- Descriptive statistics for the per-subject percentage of on-schedule infusions
- The number and percentage of subjects with ≤5 off-schedule infusions, where the denominator for the percentage will be the number of subjects who remained in the study for at least 12 months
- Descriptive statistics for the per-subject percentage of time covered by prophylaxis, calculated as 100 x (observation period [minutes] - time not covered by prophylaxis [minutes]) / (observation period [days] x 1440 minutes/day), where time not covered by prophylaxis [minutes] is calculated as the sum of all periods exceeding the planned infusion interval after each prophylactic infusion

5.8.2 Related Definitions and Derivations

5.8.2.1 Identification of Missed and Off-Schedule Doses

According to the Protocol Section 8.6.4.3.1,

> "If 1 infusion of IP is missed, the subject may administer the IP as soon as possible. The subject should adhere to their treatment scheme ensuring a minimum interval of 12 hours between this and the previous IP infusion."

In other words, if a subject does not receive a planned dose at the date/time it is scheduled, the acceptable time frame for an **off-schedule infusion** to be given in place of the scheduled infusion is **up until 12 hours before the next scheduled infusion.** If the

off-schedule dose is given within this interval (**up until 12 hours before the next scheduled infusion**), the subject will be considered as "**had an infusion during the required interval**", however, this incident will be recorded in PD log. If the infusion is not administered in this interval, it will be counted as a missed infusion (i.e., a missed dose) and the time from the missed target date to administration of the next scheduled infusion will be counted as time without prophylactic coverage.

5.9 Protocol Deviations

Protocol deviations will be recorded in the IQVIA CTMS and will be classified as critical, major, or minor. The CRO and sponsor will review the protocol deviations and their classification for accuracy throughout the study and before final database lock. Confirmed critical, major and minor protocol deviations will be documented in the Protocol Deviations tracker for the study. A multidisciplinary review of the protocol deviations by representatives of Biostatistics, Data Management and Clinical Development (including medical monitors/advisors) teams from both IQVIA and the Sponsor will be performed prior to any analysis which uses the protocol deviations.

Deviation categories will be included as part of the CTMS protocol deviations log and (per the agreed protocol deviation management plan) may include any of the following categories:

- Informed consent
- Eligibility and entry criteria
- Concomitant medication criteria
- Laboratory assessment criteria
- Study procedures criteria
- Serious AE criteria
- Visit schedule criteria
- Investigational product compliance
- Efficacy criteria

- Administrative criteria
- Source document criteria
- Regulatory or ethics approval criteria
- Other criteria.

For any criteria for protocol deviations that can be completely implemented by a computer program, the detailed algorithm will be agreed upon. Details of such algorithms will be included in the derived dataset specifications and finalized before final database lock.

Changes to the procedures or events, which may impact the quality of the PK data, will be considered significant protocol deviations for the PKAS evaluation and will be described within the clinical study report. These changes or events will include any circumstances that will alter the evaluation of the PK. Example of protocol deviations that are important to PK are:

- Sample processing errors that lead to inaccurate bioanalytical results
- Inaccurate dosing on the day of PK sampling due to administration incidences or lack of compliance to the protocol
- Dosing time (start and/or stop time of infusion) not available
- Sample drawn date and time not available
- Missing PK samples at important phases of the PK profile
- Inadequate washout period prior to IP administration

Affected data will be evaluated by the pharmacokineticist to determine whether they can be included in the PK analysis. Subjects and/or data with important deviations or other data issues that are not included in the PKAS will be reported in listings, along with the reason for exclusion. Other changes to the procedures or events which do not impact the quality of the PK data will not be considered significant protocol deviations for the

evaluation of PK. A common example of a non-significant protocol deviation is a deviation from the prespecified blood collection times.

Critical/major/minor protocol deviations will be summarized by category for each subject group and overall in the SAF. Protocol deviations will be listed for the SAF.

6. EFFICACY ANALYSES

Only the EDC eCRF bleeding episode data will be used in statistical analyses of efficacy. The eDiary Bleeding episode data is source data only and will not be combined with the EDC eCRF data for analysis purposes. The handling of infusion data was addressed in Section 5.7.

All efficacy analyses will be performed on the first 12 months of data and on all study data through the end of the study in the FAS. The baseline (historical) annualized bleeding rates will be based on bleeding episodes that occurred prior to taking the first dose of IP. Baseline for any efficacy assessment which is expected to be completed at a specified timepoint (e.g., a questionnaire) will be defined as the last observed value for the efficacy assessment prior to taking the first dose of IP (based on dates or date/times).

No statistical testing is planned. Proportions will be expressed as percentages in all tables. Confidence intervals (CIs) for percentages will be 2-sided 95% Clopper-Pearson (i.e., exact binomial) CIs, unless stated otherwise.

6.1 Analyses of Primary Efficacy Endpoint

The primary analysis of the primary endpoint will be the estimation of the ABR for treated spontaneous BEs while on prophylactic treatment with rVWF (vonicog alfa), as derived in Section 12.5.2, overall and by subject group (on demand or switch), based on the FAS. Data through Month 12 will be used. No formal statistical hypothesis testing is planned.

The baseline ABR for treated spontaneous BEs for each subject group will be based on historical data collected from each enrolled subject on the *Von Willebrand Treatment and Bleed History eCRF* and derived per Section 12.5.2. Data for estimation of the on-study ABR for treated spontaneous BEs will be taken from the *Bleeding Episode Details eCRF* in the EDC.

In general, if a bleed occurs more than 24 hours following resolution of a current bleed, or at a different anatomical location, it will be counted as a separate "new" bleeding episode [BE]. However, this determination will be made by the investigator.

The ratio of the two ABRs (on-study / historical) for treated spontaneous BEs will be estimated within each subject group using a generalized linear mixed-effects model (GLMM) with the negative binomial distribution as a family and with a logarithmic link function (the default). The dependent variable will be the number of unique bleeds for each subject by observation period (during OPE, historical). The independent term in the model will be period. Model options will include the logarithm of the duration of the observation period (in years) as an offset. The ABR ratio together with its two-sided, 95% Wald CI will be presented in exponentiated form for each subject group. Sample SAS code for performing the analysis is presented in Section 16.1.

All subjects in the FAS will be included in these analyses. If a FAS subject had no treated spontaneous bleeds and the ABR estimation routine results in a missing ABR, then an ABR of 0 will be assigned to the subject prior to analysis. If an analysis fails to converge because many bleed counts were zero, the estimate will be presented with no CI.

If the GLMM fails to converge for another reason, the IQVIA and sponsor statisticians will confer regarding the most appropriate course of action. One possible course of action may be to calculate the ratio of the on-study ABR and the historical ABR as the mean of the subject ratios (study period ABR/historical ABR) for subjects with a historical ABR different from 0. The corresponding 95% confidence interval might be reported as well.

6.1.1 Sensitivity Analyses of Primary Efficacy Endpoint

The analyses which are described as primary analyses (Section 6.1) will be conducted in the FAS using all data collected during the study (through completion/discontinuation) as sensitivity analyses.

6.1.2 Supplemental Analyses of Primary Efficacy Endpoint

The analyses which are described as primary analyses (Section 6.1) will be conducted in the MFAS and PPAS as supplemental (supportive) analyses.

6.2 Analyses of Secondary Efficacy Endpoints

Data from secondary efficacy endpoints will be summarized for each subject group and overall (when applicable) using the first 12 months of data for the FAS, unless otherwise

specified. Mean, standard deviation, median, range, quartiles will be calculated for continuous endpoints. Proportions will be calculated for categorical endpoints and expressed as percentages in tables and listings. Clopper-Pearson CIs at the 95% level will be provided for percentages when appropriate.

Secondary endpoints for the efficacy of prophylactic treatment with rVWF (vonicog alfa) will be calculated and summarized by subject group as follows:

- ABR reduction success for OD subjects based on treated spontaneous BEs, as defined in Section 12.5.4, will be presented together with the corresponding two-sided 95% Clopper-Pearson CI for the percentage. [Note: Statistics using FAS data through completion/discontinuation from study will also be provided.]

- ABR preservation success for switch subjects based on treated spontaneous BEs, as defined in Section 12.5.5, will be presented together with the corresponding two-sided 95% Clopper-Pearson CI for the percentage. [Note: Statistics using FAS data through completion/discontinuation from study will also be provided.]

- The number and percentage of subjects who had ABR based on treated spontaneous BEs in categories of 0, >0 through 2, >2 through 5, >5 will be presented by subject group and overall. [Note: Statistics using FAS data through completion/discontinuation from study will also be provided.]

- The ABR for treated spontaneous BEs during the historical and rVWF (vonicog alfa) prophylaxis periods and the change in ABR between the two periods will be summarized in each subject group.

- The analyses of secondary efficacy endpoints related to consumption of study drug (i.e., total number of infusions, average number of infusions per week during prophylactic treatment with rVWF (vonicog alfa), and total weight-adjusted consumption of rVWF (vonicog alfa) in up to 12 months of prophylactic treatment) are described with the analysis of the IP exposure data (Section 5.7).

- ABR for treated spontaneous BEs by location of bleeding (gastrointestinal [GI], epistaxis, joint bleeding, menorrhagia, oral and other mucosa, muscle and soft tissue, etc.) while on prophylactic treatment with rVWF (vonicog alfa). Section 12.5 provides more information about the handling of menstrual bleeding and menorrhagia.

6.2.1 Sensitivity Analyses of Secondary Efficacy Endpoints

The analyses described in Section 6.2 will be conducted in the FAS using all data collected during the study (i.e., through study completion/discontinuation) as a sensitivity analysis.

6.2.2 Supplemental Analyses of Secondary Efficacy Endpoints

All analyses described in Section 6.2 will be conducted in the MFAS and PPAS as supplemental (supportive) analyses.

Additionally, the ABR for BEs by study period and the change in ABR for BEs between the two periods will be summarized for bleeds due to any cause (i.e., all causes) and by cause of bleeding, subject group, and overall. Descriptive statistics will be provided.

Also, a summary table of the number of bleeding episodes by study period, cause of bleeding, and severity will be provided. For each cause of bleeding, the total number of recorded episodes and the number and percentage of episodes by severity level (within cause) will be presented, overall and by cohort. Both the historical and on-study data will be characterized.

Data related to menstrual bleeding during the historical period will be identified and remapped as described in SAP Section 12.5.1 prior to performing any analyses by cause of bleed.

A missing ABR will be assigned as an ABR of 0 for the subject for the relevant cause of bleeding, bleed location, or bleed severity at the relevant location.

6.3 Multiplicity Adjustment

Not applicable. No statistical testing is planned.

6.4 Analyses of Exploratory Endpoints

6.4.1 [redacted]

[redacted]

[redacted]

6.4.1.1 [redacted]

[redacted]

6.4.2 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.4.3 [redacted]

[redacted]

6.5 Subgroup Analyses

Subjects with VWD Type 3: A few tables will be produced (or will include statistics) for FAS subjects with VWD Type 3. These will include:

- History of bleeding episodes
- Comparison of annualized bleeding rates for treated spontaneous BEs through Month 12 (same methods as primary efficacy analysis)
- Descriptive statistics for annualized bleeding rates (ABR) for BEs through Month 12, by study period and cause of bleed
- The annualized bleeding rate reduction success based on treated spontaneous BEs in on-demand subjects using data through Month 12
- The annualized bleeding rate preservation success based on treated spontaneous BEs in switch subjects using data through Month 12
- Investigator assessment of efficacy of the treatment of spontaneous bleeding episodes using data through Month 12
- Number of infusions and total weight adjusted consumption of rVWF and ADVATE per spontaneous bleeding episode, using data through Month 12.

Too few subjects with other types of VWD are anticipated to support meaningful summary statistics. Data for these subjects will be presented in the listings.

Subjects Who Had Surgery: Some data were collected only from subjects who entered the current study from a prior surgical protocol and/or who underwent concomitant surgery during the current protocol. Any tables, listings, or figures which present these data will be identified appropriately in the title. All data from these subjects will be listed. Tables may be produced if at least 5 subjects had a surgery. Any denominators for percentages on these tables will be based on subjects in the surgery subset, unless otherwise specified.

7. SAFETY ANALYSIS

The safety analysis will be performed using the SAF. Safety variables include AEs *[Adverse Event eCRF]*, clinical laboratory results *[Central laboratory eCRFs, electronic files]*, vital signs *[Vital Signs eCRF]*, and electrocardiogram (ECG) overall interpretation *[ECG eCRF]*. For each safety variable, the last value collected before the first dose of IP will be used as baseline for all analyses of that safety variable.

All AE summaries will be performed by the last IP received prior to the start of the AE. If the last IP received prior to the start of the AE was both rVWF (vonicog alfa) and ADVATE (rFVIIII, octocog alfa) administered in sequential order, then the AE will be counted towards both IPs.

7.1 Adverse Events

7.1.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a subject administered IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom (e.g., rash, pain, discomfort, fever, dizziness, etc.), disease (e.g., peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, regardless of whether it is considered causally related to the IP.

7.1.2 Coding of Adverse Events

Adverse events will be coded to a system organ class (SOC) and preferred term (PT) using the version of the Medical Dictionary for Regulatory Activities (MedDRA) which is specified in the data management coding guidelines.

7.1.3 Treatment-Emergence

See Section 12.4.3 for a generalized description that applies to AEs as well as other data classes.

7.1.4 Treatment-Related AEs

The investigator will provide an assessment of AE causality on the eCRF. TEAEs will be considered as related to IP if "Probably Related" or "Possibly Related" is indicated.

7.1.5 Temporally-Associated AEs

Temporally associated AEs are defined as AEs that begin during infusion or within 24 hours (or 1 day where time of onset is not available) after completion of the most recent infusion prior to onset, irrespective of being related or not related to treatment. All temporally-associated AEs are TEAEs.

Temporal association to ADVATE and to rVWF is collected on the eCRF only when the AE start date or time is missing. For TEAEs with complete start date-times, temporal association must be derived as the time since last IP administration, where last IP administration is defined as the IP immediately preceding the start of the AE.

If time is available for both the start date of the AE and the IP administration, then time since last IP administration will be calculated as:

Time since last administration (hours) = AE start date-time – Dose start date-time

If the result is ≤ 24 hours, then the time since last administration will be presented in hours. If time is missing from either the start date of the AE or the IP administration, or the time since last administration is > 24 hours, then the results will be presented in days, calculated as:

Time since last administration (days) = AE start date – Dose start date + 1.

7.1.6 Adverse Events of Special Interest

Adverse events of special interest (AESI), which include severe allergic reactions, hypersensitivity reactions and thromboembolic events, are monitored throughout the study and identified on the *Adverse Event* eCRF by the investigator.

Protocol Section 13.4.2.3 specifies that the final analysis and summarization of TEAEs of special interest will be conducted based on search criteria (e.g., standardized MedDRA queries [SMQ]) that will be determined prior to database lock. The SMQs that will be implemented for this study are:

- Hypersensitivity SMQ (Narrow Scope)
- Anaphylactic Reaction SMQ (Narrow Scope) and severe Hypersensitivity reactions as identified by the investigator.
- Angioedema SMQ (Narrow Scope)
- Embolic and Thrombotic Events SMQ (Narrow Scope) plus any investigator-identified events

Finally, the development of antibodies against VWF is a rare complication of VWD replacement therapy. For immunogenicity analysis, frequency counts and proportions will be calculated for subjects with the occurrence of neutralizing (inhibitory) antibodies to VWF and FVIII, occurrence of binding antibodies to VWF and FVIII, and occurrence of binding antibodies to CHO proteins, mouse immunoglobulin G (IgG) and rFurin. Further details of analyses related to immunogenicity are provided in Section 7.2.6.

7.1.7 Counting Methods

If more than 1 AE with the same PT occurs for a subject within a specified observation period, then the subject will be counted only once for that PT during that observation

period, using the most severe and most related occurrence for summaries by severity and by relationship to IP, respectively.

7.1.8 Duration of AEs

The duration of an AE will be calculated without imputation as stop date-time minus start date-time plus 1. The duration will be presented in hours if the result is ≤24 hours. If the result is >24 hours, or either the start or stop time is missing or incomplete, then the result will be presented in integer days calculated as stop date minus start date plus 1. If either the start date or stop date is partial or completely missing, no duration will be calculated.

7.1.9 Planned Analyses

In this study, adverse events may be treatment emergent following rVWF administration, ADVATE administration, or administration of both together. Therefore, AE analyses in this study could be conducted on all TEAEs or based on IP TE status (i.e., performed for rVWF TEAEs and ADVATE TEAEs separately).

The following analyses will be produced overall, for AEs that were treatment-emergent following any IP. A few analyses will also be done by IP TE status (separate analyses of rVWF-emergent AEs and ADVATE-emergent AEs, where specified):

- Overall AE summary: The data in the overall summary will be presented by subject group and overall. The summary will be created for any (all) TEAEs and by IP TE status (separate analyses of rVWF TEAEs and ADVATE TEAEs). In each overall summary table, the number and percentage of subjects with TEAEs and the number of events will be presented for the following groups of events:

    - Any TEAEs
    - Serious TEAEs (STEAEs)
    - TEAEs/STEAEs related to IP (rVWF, ADVATE) based on investigator assessment of causality
    - TEAEs/STEAEs related to study procedures
    - TEAEs leading to discontinuation of IP (rVWF, ADVATE)
    - TEAEs leading to discontinuation from study
    - TEAEs leading to death
    - Life-threatening TEAEs
    - Severe TEAEs
    - Temporally associated TEAEs/STEAEs
    - Thromboembolic TEAEs

- Thromboembolic TEAEs related to IP (investigator's assessment)
- Thromboembolic STEAEs
- Thromboembolic STEAEs related to IP (investigator's assessment)
- Severe allergic reaction TEAEs/STEAEs
- Severe hypersensitivity reaction TEAEs/STEAEs

- Summaries of TEAEs by PT only, in descending order of overall incidence for:
  - All TEAEs
  - TEAEs occurring in ≥10% of subjects
- Summaries by SOC and PT: The number and percentage of subjects reporting AEs and the number of events will be tabulated by subject group and overall. SOC will be presented alphabetically. PT within SOC will be presented by descending incidence. The analysis will be done for the following groups of AEs:
  - Any TEAEs
  - Any rVWF treatment-emergent AEs
  - Any ADVATE treatment-emergent AEs
  - TEAEs that occurred in ≥10% of subjects
  - TEAEs considered related to rVWF by investigator
  - TEAEs considered related to ADVATE by investigator
  - TEAEs considered related to study procedures by investigator
  - STEAEs
  - TEAEs leading to withdrawal of rVWF
  - TEAEs leading to withdrawal of ADVATE
  - TEAEs leading to death
  - TEAEs leading to discontinuation from study
  - Life-threatening TEAEs
  - Treatment-emergent AESIs
  - rVWF treatment-emergent AESIs
  - ADVATE treatment-emergent AESIs
  - TEAEs temporally associated with rVWF
  - TEAEs temporally associated with ADVATE
  - non-serious TEAEs considered to be related to rVWF by the investigator
  - non-serious TEAEs considered to be related to ADVATE by the investigator

- Summaries by SOC, PT, and maximum severity: SOC will be presented alphabetically. PT within SOC will be presented by descending incidence in the combined subject groups (where applicable). Within PT, events will be sorted by maximum severity (mild, moderate, severe and total). The number and percentage of subjects reporting AEs and the number of events will be tabulated by SOC, PT and maximum severity, overall and by subject group, for the following set(s) of events:

    - All TEAEs
    - rVWF treatment-emergent AEs
    - ADVATE treatment-emergent AEs

Summaries by demographic subgroup: The following safety tables will be produced by region (US, non-US), gender (male, female), and age group (<65, ≥65). The number and percentage of subjects reporting AEs and the number of events will be tabulated by subject group and overall. Where applicable, SOC will be presented alphabetically. PT within SOC will be presented by descending incidence.

- Overall treatment-emergent adverse events by gender
- Overall treatment-emergent adverse events by age group
- Overall treatment-emergent adverse events by region
- Treatment-emergent adverse events by SOC, PT and gender
- Treatment-emergent adverse events by SOC, PT and age group
- Treatment-emergent adverse events by SOC, PT and region

No summaries by race or ethnicity are planned due to the small sample size and low degree of variability in these characteristics in this study.

Listings: A listing of all AEs will be presented by subject group and subject identifier. Subject identifier, age, sex, system organ class / preferred term / reported term of the AE, duration, severity, seriousness, action taken, outcome, causality assessment by investigator, onset date, stop date and medication or non-drug therapy to treat the AE will be presented. If recorded, the concomitant medications used to treat the AE, and/or the associated medical history condition, will be cross-referenced on the listing. Separate listings of serious AEs, AEs which led to discontinuation, AEs which led to death, temporally associated AEs, thromboembolic events, and hypersensitivity reaction events will be produced.

7.2 Clinical Laboratory Data

Descriptive statistics for clinical laboratory values as obtained from the central laboratory (in SI units) and changes from baseline at each planned assessment time point will be presented by subject group. Results obtained from local laboratories will not be included in summaries.

All laboratory data (including tests from unscheduled and event-related samples) will be listed for the SAF.

7.2.1 Clinical Chemistry

Blood will be obtained for assessment of clinical chemistry parameters on the schedule specified in Protocol Supplement 20.3, Clinical Laboratory Assessments.

Descriptive statistics for clinical laboratory values (in SI units), changes from baseline, and percent changes from baseline at all planned non-PK assessment timepoints will be presented by subject group and overall for the following clinical laboratory variables: sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP) and bilirubin. Clinical laboratory results obtained during PK assessment timepoints will not be included in clinical laboratory data outputs, but in PK-specific outputs as described in Section 8.

Shift tables based on evaluation against the reference range (low, normal, high) at baseline and post-baseline assessment time points will be presented for the same list of planned parameters, by subject group and overall. The number and percentage of subjects in each post-baseline category will be based on the number of SAF subjects who had both baseline and post-baseline data for a parameter within a specified timepoint and subject group.

Laboratory values will be evaluated for clinical significance by the investigator. Clinically significant results may be recorded as AEs, at the discretion of the investigator. The number and percentage of subjects with clinically significant abnormal values on any parameter and by parameter will be tabulated for the study overall (i.e., at any time during the treatment period), at each planned timepoint, by subject group and overall. All available data from both scheduled and unscheduled assessments will be used. The percentages will be calculated relative to the number of subjects with available baseline values and at least 1 post-baseline assessment in a specified analysis window. The

numerator will be the total number of subjects with at least 1 clinically significant post-baseline laboratory value in the specified analysis window.

Only central laboratory data will be used in the summaries. All laboratory data will be listed for the SAF. An additional supportive listing of subjects with post-baseline clinically significant values will be provided including the subject number, site, baseline and post-baseline clinically significant values.

7.2.2 Hematology

Hematology assessments will be performed on the same schedule as the clinical chemistry and will be analyzed using the same methods (Section 7.2.1). The following parameters will be analyzed:

- Complete blood count, which includes hemoglobin, hematocrit, erythrocytes (i.e. red blood cell (RBC) count), mean corpuscular volume, (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell (WBC) count)
- Differential, which includes basophils, eosinophils, lymphocytes, monocytes, neutrophils
- Platelet counts

7.2.3 Coagulation

The coagulation panel includes prothrombin time (PT), International Normalized Ratio (INR) and activated partial thromboplastin time (aPTT). These parameters are planned to be assessed pre- and post-infusion throughout the study and in the case of thromboembolic events, as described in Protocol Section 20.3.

Screening results will be summarized with the subject baseline characteristics using descriptive statistics by subject group and overall. Descriptive statistics for observed values (in SI units) and changes from baseline at planned timepoints will be presented by subject group and overall. Shift tables from baseline to post-baseline are not planned. Results obtained during PK assessment will not be included in clinical laboratory data outputs, but in PK specific outputs as described in Section 8.

7.2.4 Urinalysis

A dipstick urinalysis at screening is planned. The urinalysis includes assessments for erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite and pH (screening only). All urinalysis results will be listed. No summary is planned.

[Note: No post-baseline urinalysis is planned; however, any treatment-emergent, clinically important changes in urinary parameters which may be identified from unscheduled urine samples are expected to be reported as adverse events.]

7.2.5 Viral Serology

Viral serology is planned only at screening. The tests include Hepatitis A antibody (total), Hepatitis A antibody (IgM), Hepatitis B surface antibody, Hepatitis B Core Ab (total), Hepatitis B surface antigen, Hepatitis C virus antibody, Parvovirus B19 and HIV-1/HIV-2 antibodies. Descriptive statistics have been included with the subject characteristics at screening. All viral serology results will be listed.

[Note: No post-baseline viral serology testing is planned; however, any treatment-emergent, clinically important changes in viral serology which may be identified from unscheduled lab samples are expected to be reported as adverse events.]

7.2.6 Immunogenicity

Frequency counts and percentage of subjects who had an occurrence (i.e., a positive result) of neutralizing (inhibitory) antibodies to VWF and FVIII, occurrence of binding antibodies to VWF and FVIII, and occurrence of binding antibodies to CHO proteins, mouse immunoglobulin G (IgG) and rFurin. Completely missing antibody data during the treatment period will be interpreted as no new development of antibodies.

The analyses will be performed using the SAF. Results will be presented by subject group and overall. All sample results will be listed.

7.2.7 Pregnancy Test

A pregnancy test for females of child-bearing potential will be performed at the local laboratory, primarily from urine. If no urine sample is available, the pregnancy testing will be done from serum.

All planned and unplanned pregnancy tests will be listed. A separate listing of subjects with positive pregnancy test results (if any) will be provided.

7.3 Vital Signs

Vital signs will be assessed pre- and post-infusion at each visit, within 30 minutes before and after IP administration, if not stated otherwise:

- Pulse rate: Pulse rate (beats/min) will be measured at the distal radial arteries under the same conditions as above
- Blood pressure: Systolic and diastolic blood pressure (mmHg) baseline measurements will be measured after a 10-minute rest in the supine/semi-recumbent position
- Height (cm) (Screening only)
- Weight (kg) (pre-infusion only)
- Temperature: Body temperature in degrees Centigrade (°C) or degrees Fahrenheit (°F) may be determined by oral, rectal, axillary, or tympanic measurement at the discretion of the investigator. [Note: The same method is expected to be used for all measurements in 1 subject.
- Respiratory rate: Respiratory rate (breaths/min) will be measured over a period of 1 minute under the same conditions as above.

Descriptive statistics for vital signs (e.g., pulse rate, systolic and diastolic blood pressure, height, body weight, body temperature and respiratory rate) as reported on the *Vital Signs* eCRFs at each planned timepoint and post-dose changes from baseline at each planned post-baseline visit will be presented by subject group and overall.

Vital sign values will be considered potentially clinically significant (PCS) if they meet both the observed value criteria and the change from baseline criteria listed in Table 2. The number and percentage of subjects with PCS post-baseline values will be tabulated by subject group and overall. Percentages will be calculated relative to the total number of subjects with at least 1 post-baseline vital sign value. A listing of subjects with post-baseline PCS values will be provided including the subject number, site, baseline, and post-baseline PCS values.

Table 2: Criteria for Potentially Clinically Significant Vital Signs

		Criteria[a]	
Vital Sign Parameter	**Flag**	**Observed Value**	**Change from Baseline**
Systolic blood pressure (mmHg)	High	≥180	Increase of ≥20
	Low	≤90	Decrease of ≥20
Diastolic blood pressure (mmHg)	High	≥105	Increase of ≥15
	Low	≤50	Decrease of ≥15
Pulse rate (beats per minute)	High	≥120	Increase of ≥15
	Low	≤50	Decrease of ≥15
Weight (kg)	High	-	Increase of ≥7%
	Low	-	Decrease of ≥7%

[a] A post-baseline value is considered as a potentially clinically significant value if it meets both criteria for observed value and change from baseline.

Vital sign values will be evaluated for clinical significance by the investigator. Clinically significant results may be recorded as AEs, at the discretion of the investigator.

All vital signs data will be listed for the SAF.

7.4 Electrocardiogram

Electrocardiogram interpretation by the Investigator as entered on the *Electrocardiogram* eCRF will be summarized by subject group and listed for the SAF.

A shift table from baseline to each planned visit will be presented.

7.5 Other Safety Data

Not applicable.

8. PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS

The derivation of PK/PD parameters will be the responsibility of the clinical pharmacokineticist at IQVIA. Production of the PK/PD summaries and data listings will be the responsibility of the study Biostatistician at IQVIA. IQVIA Standard Operating Procedures and Work Instructions will be used as the default methodology, unless otherwise specified.

All summaries and analyses of the pharmacokinetic/pharmacodynamic data will be based on the Pharmacokinetic/Pharmacodynamic Analysis Set (PKAS) defined in Section 4.5.

8.1 Planned Sampling

PK/PD will be assessed twice for all subjects. PK/PD parameters at steady state will be assessed shortly after reaching steady state for switch subjectsandsubjects and at the end of the study for both switch and on-demand subjects , all based on the longer interval of the irregular dosing intervals employed.

For OD subjects, an initial PK/PD assessment using a dose of 50 IU/kg ± 5 IU/kg rVWF:RCo will be performed at the baseline visit. A washout period of at least 5 days is required before the infusion of rVWF (vonicog alfa) for PK assessment can be administered. At the 12-month (± 2 weeks) visit, a steady state PK analysis will be performed based on the longer interval of the irregular dosing intervals employed. For both assessments, blood samples will be drawn within 30 minutes pre-infusion and at 11 time points post-infusion (15 ± 5 minutes, 30 ± 5 minutes, 60 ± 5 minutes, 3 ± 0.5 hours, 6 ± 0.5 hours, 12 ± 0.5 hours, 24 ± 0.5 hours, 30 ± 2 hours, 48 ± 2 hours, 72 ± 2 hours and 96 ± 2 hours). VWF activity will be determined using the VWF: RCo, VWF: CB and the VWF: Ag assays. Endogenous FVIII activity will be measured using the 1-stage clotting assay to assess the pharmacodynamics of rVWF (vonicog alfa).

For pdVWF switch subjects, the initial PK/PD assessment using the subject's individualized dose will be performed shortly after reaching steady state, which is estimated to occur approximately 11 days after the 1st prophylactic dose for most subjects. To fit any logistical requirements, samples for PK analysis can be taken after prophylaxis dose #5-6. Whenever possible, sample collections should be during the longer partial interval of the alternating irregular dosing intervals. An example is shown in Table 3.

Table 3. Example of Irregular Dosing Intervals with Preferred PK/PD Sampling Schedule

Date	Weekday	Dose number	Interval (days)	Time from first dose in hours
8.1.18 8:00	Monday	1	0	0
12.1.18 8:00	Friday	2	4	96
15.1.18 8:00	Monday	3	3	168
19.1.18 8:00	Friday	4	4	264
22.1.18 8:00	Monday	5	3	336
26.1.18 8:00	Friday	6	4	432

After reaching the steady state, the PK assessment can be done at Dose 5 to allow the 96h post-infusion sampling, before the next scheduled dose (for patients on a twice per week dosing schedule).

A similar 2nd full PK/PD profile will be assessed at the end of the study, i.e. 12 month ± 2 weeks visit with an IP infusion at the same dosing partial interval (96h interval in this case). Blood samples will be drawn within 30 minutes pre-infusion and at 11 timepoints post-infusion (15 ± 5 minutes, 30 ± 5 minutes, 60 ± 5 minutes, 3 ± 0.5 hours, 6 ± 0.5 hours, 12 ± 0.5 hours, 24 ± 0.5 hours, 30 ± 2 hours, 48 ± 2 hours, 72 ± 2 hours, 96 ± 2 hours). If the dosing interval for a specified switch subject wouldn't allow for collection of the full set of 11 post-infusion samples, the 96-hour sampling timepoint can be omitted, but it is critical that the assessments are at the same partial interval, thereby same number of sampling timepoints, for the 1st and 2nd PK/PD for each subject.

If a subject should experience a bleeding episode during the PK/PD assessment, then no subsequent blood sample will be drawn in that specific PK/PD period. The guidance provided in Protocol Section 8.6.4.4 must be followed for the treatment of the bleeding episode. Once recovered, the subject is eligible to repeat the PK/PD assessment. In case of surgery or bleeding, the PK/PD assessment should be performed after 11 days after 1st prophylactic dose after restart of prophylactic regimen.

Listings of the IP infusion data will include information about the washout period, infusion date, age of subject at time of first dose, planned total rVWF dose (IU), planned rVWF volume to be administered, actual total units of rVWF infused (IU), actual volume of rVWF administered (mL), actual potency (IU), number of vials used, rVWF lot number, infusion start time, infusion end time, infusion rate (mL/min), infusion interruptions or rate changes, and the reasons for any interruption or rate change.

A separate listing of the PK/PD results will include the date and time of the last previous infusion, the PK/PD planned timepoint, date and time of PK/PD blood draw, the analyte(s) and the result(s).

8.2 Below Limit of Quantitation (BLQ) Values

VWF/FVIII:C activities that are BLQ will be treated as zero for the computation of descriptive statistics. For PK parameter calculation, pre-infusion samples that are BLQ will be assigned a numerical value of zero. BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating PK parameters. If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration), it will be set to zero. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by setting them to missing, unless otherwise warranted by then concentration-time profile.

8.3 Pharmacokinetic and Pharmacodynamic Parameters

8.3.1 General

PK/PD parameters will be derived using noncompartmental methods using the IV infusion model (Model 202) and linear-up/log-down trapezoidal rule with Phoenix® WinNonlin® Version 8.0 (Certara L.P. Princeton, New Jersey, US). The PK/PD parameter analysis will use actual elapsed time from the start of infusion rather than scheduled sampling times, wherever possible, and actual infusion duration. A deviation from the protocol specified blood sampling drawing time window will not be a reason to exclude an observation from the analysis. Samples with unknown actual and planned collection date/time or where the concentration could not be determined, or where biological implausible will be excluded from the analysis.

8.3.2 Pre-infusion Correction

8.3.2.1 PK/PD concentration correction after a washout for OD subjects

Pre-infusion samples that are BLQ will be assigned a numerical value of zero. Missing VWF pre-infusion concentration levels (VWF:RCo, VWF:Ag or VWF:CB) for Type 3 subjects will be set to zero. Handling of other missing pre-infusion concentration levels will be decided on a case-by-case basis and described in a Note-to-File or the study report.

Except for Type 3 subjects, all post-infusion PK/PD measurements will be adjusted for pre-infusion values should the pre-infusion measurement not be BLQ. The pre-infusion correction will be performed as:

$$C_{corrected,t} = C_{measured,t} - C_{measured,pre-infusion}.$$

Any negative pre-infusion corrected concentrations will be set to missing.

For Type 3 subjects with detectable pre-infusion concentration values, validity of pre-infusion values will be verified by data management and/or the laboratory and if correct, values will be corrected for pre-infusion values using the following formula:

$$C_{corrected,t} = \left(1 - \frac{C_{measured,pre\text{-}infusion}}{C_{max,measured}}\right) \times C_{measured,t}$$

where $C_{measured,pre\text{-}infusion}$ is the pre-infusion concentration, $C_{max,measured}$ is the maximum concentration measured post dose and $C_{measured,t}$ is the measured concentration at time t. Following baseline-correction, any pre-infusion value will be set to zero.

Concentration correction for FVIII only based on the first equation regardless of VWD types.

8.3.2.2 PK/PD concentration correction at steady state for OD subjects and for both PK infusions of switch subjects

There will be no PK/PD concentration correction at steady state for OD subjects and for both PK infusions of switch subjects.

8.3.3 Calculated Parameters

The following PK/PD parameters, based on PK/PD concentration/activity with and without baseline correction after a washout for non-steady state conditions for OD subjects only, will be calculated for VWF:RCo, VWF:Ag and VWF:CB, where possible:

$AUC_{0-\infty}$	Area under the concentration versus time curve from 0 extrapolated to infinity after a single dose using linear Trapezoidal Linear/Log interpolation calculation method; calculated as $AUC_{last} + \frac{C_{last}}{\lambda_z}$ where

	C_{last} is the estimated concentration of the last quantifiable time point. (single dose initial PK assessment only)
$AUC_{0-\infty}/D$	Dose-normalized $AUC_{0-\infty}$ (single dose initial PK assessment only)
$AUC_{0-\text{tlast}}$	Area under the concentration versus time curve from 0 to the last quantifiable sample after a single dose using linear Trapezoidal Linear/Log interpolation calculation method
$AUC_{0-\text{tlast}}/D$	Dose-normalized $AUC_{0\text{-}96hr}$
CL	Apparent total body clearance of the drug from blood, calculated as $\frac{\text{Dose(IU/kg)}}{AUC_{0-\infty}}$
C_{max}	Maximum observed concentration in a concentration-time profile after a single dose; obtained directly from the concentration-time data.
C_{max}/D	Dose-normalized C_{max}
$C_{predose}$	Concentration at predose
IR at C_{max}	Incremental recovery, calculated as $\frac{C_{max}-C_{pre\text{-}infusion}}{Dose\ (IU/kg)}$ where C_{max} is the observed maximum concentration before correcting for pre-infusion values
MRT	Mean residence time; calculated as $\frac{AUMC_{0-\infty}}{AUC_{0-\infty}} - \frac{TI}{2}$ where TI is the time duration of infusion, where AUMC is the area under the first moment curve.
$t_{\frac{1}{2}}$	Apparent terminal half-life; calculated as $\frac{\ln 2}{\lambda_z}$
t_{max}	Minimum time to reach the C_{max} concentration after a single dose
V_{ss}	Apparent volume of distribution at steady state, calculated by $MRT \times CL$

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

$t_{\frac{1}{2}}, Interval$	The time interval of the log-linear regression to determine λ_z
$t_{\frac{1}{2}}, N$	Number of data points included in the log-linear regression analysis to determine λ_z
$R_{sq_{adjusted}}$	Goodness-of-fit statistic for calculation of λ_z (coefficient of determination)
$\%AUC_{ex}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation

For FVIII:C, after a washout (measured by the 1-stage clotting assay), only $C_{predose}$ C_{max}, t_{max} and AUC_{0-last} will be calculated, if possible. Other parameters may be added at the discretion of the pharmacokineticist.

The following PK parameters, based on serial PK assessments at steady state for OD subjects and for both PK infusions of switch subjects, will be calculated for VWF:RCo, VWF:Ag and VWF:CB, where possible:

$AUC_{0-tau,ss}$	Area under the concentration versus time curve from over a dosing interval at steady-state
$AUC_{0-tau,ss}/D$	Dose-normalized $AUC_{0\text{-}tau,ss}$
$C_{max,ss}$	Maximum observed concentration in a concentration-time profile at steady state; obtained directly from the concentration-time data
$C_{max,ss}/D$	Dose-normalized $C_{max,ss}$
$t_{max,ss}$	Minimum time to reach the $C_{max,ss}$ concentration at steady state
$C_{predose,ss}$	Predose concentration at steady state
$C_{min,ss}$	Minimum concentration during the dosing interval

$C_{min,ss}/D$ Dose-normalized $C_{min,ss}$

For FVIII:C at steady state (measured by the 1-stage clotting assay), only $AUC_{0-tau,ss}$, $C_{max,ss}$, $t_{max,ss}$ $C_{predose,ss}$ and $C_{min,ss}$ will be calculated, if possible. Other parameters may be added at the discretion of the pharmacokineticist.

All PK/PD parameters will be summarized using descriptive statistics where applicable for nominal dosing regimens and sampling schemes . Descriptive statistics for PK/PD parameters will include n, mean, SD, geometric mean, % geometric CV, 95% CIs, minimum, median and maximum, except that t_{max} will be reported with n, minimum, median and maximum only.

For all subjects in the PKAS, mean and individual activity/concentration vs. nominal time curves will be displayed graphically.

8.4 Statistical Analysis of Pharmacokinetics/Pharmacodynamics

Changes in $AUC_{0\text{-}tau,ss}$, $C_{max,ss}$, and $C_{min,ss}$ over time (i.e. between initial steady state assessment and the end of the study assessment) will be evaluated using the ratio of geometric means and corresponding two-sided 95% Wald CIs for VWF:RCo, VWF:Ag, VWF:CB and FVIII:C. These analyses will be performed using a linear mixed effects model with PK/PD assessment (i.e. factor of two levels relating to the PK/PD assessment shortly after reaching steady state and the PK/PD assessment at end of study, respectively) as a fixed effect and subject as a random effect based on log-transformed PK/PD parameters. Sample SAS code is presented in Section 16.1.

The difference in $T_{max;ss}$, between first and second pharmacokinetic assessment will be summarized by the median and range (minimum to maximum) for VWF:RCo, VWF:Ag, VWF:CB and FVIII:C. A point estimate and Hodges-Lehmann CI for the log-scale difference (i.e., ratio) of the two assessments, will also be generated. Han (2008) provided an explanation of the process and sample SAS code for performing the analysis either in a macro or non-macro code environment. The sample SAS code and key explanatory points are reproduced in Section 16.1.4.

9. [redacted]

9.1 [redacted]

[redacted]

9.2 [redacted]

[redacted]

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9.3 [redacted]

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10. [redacted]

10.1 [redacted]

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- [redacted]
- [redacted]
- [redacted]

[redacted]

11. INTERIM ANALYSIS/ DATA MONITORING (REVIEW) COMMITTEE

A DMC was set up to review subject data during the trial at certain time points as defined in the DMC charter to ensure the safety and well-being of trial subjects. No formal interim analysis for efficacy will be performed.

For this study, the DMC will be composed of recognized experts in the field of VWD clinical care and research who are not actively recruiting subjects and an independent statistician. The DMC can recommend stopping a trial if it finds toxicities or if treatment is proven to be not beneficial.

For further details of the DMC, see the DMC Charter for the study.

12. DATA HANDLING CONVENTIONS

12.1 General Data Reporting Conventions

All subject data that are collected during this study will be disclosed on listings. Listings will be sorted by subject group and subject number, unless otherwise specified. In general, imputed data will not be shown on listings. If imputed values must be shown on a listing to ensure traceability or clarity of the statistical methods, these values will be clearly identified on the output.

Continuous variables will be summarized using the following descriptive statistics: the number of subjects with available data (n), mean, median, standard deviation, the 1st and 3rd.quartiles, minimum, maximum. The above descriptive statistics will only be presented if there are at least 3 results available in a group. All statistics except median will be presented if only 2 results are available in a group while only n and mean will be presented if only 1 result is available in a group.

Tables, listings and/or figures will present individual measurements, the minimum and the maximum with the number of decimals that were collected. Means (including least-square means and geometric means if applicable), medians or other quartiles and confidence limits will be presented using 1 more decimal than the collected data. Standard deviations (SD) and standard errors of the mean (SE) will be presented using 2 decimals more than the collected data.

Tables for assessments that have a predefined list of possible outcomes on the CRF will display a row or column for each possible response. For assessments that collect open-ended responses, such as general adverse events or concomitant medications, only the reported values will be tabulated.

Categorical measures will be summarized by the number (n) and percentage (%) of subjects who had a specific response. Each table, listing and figure will include a footnote which identifies the denominator used to calculate any percentages. Percentages and their confidence limits will be presented using 1 decimal. Any cell count of zero will be presented as ‘0’; the associated percentage of ‘(0.0%)’ will not be presented. Any cell percentage of 100% will be presented without decimals.

All values will be rounded using the SAS® function ROUND (where applicable).

All PK concentrations/activities will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory regardless of how many significant figures or decimals the data carry. Unrounded derived PK data will be considered the source data for the calculation of descriptive statistics. Derived PK parameters will be rounded for reporting purposes in by-subject listings. For most derived PK parameters, 3 significant digits will be used as the standard rounding procedure, with the following exceptions:

- Parameters directly derived from source data (e.g., C_{max}) will be reported and analyzed using the same precision as the source data.
- Parameters derived from actual elapsed sample collection times (e.g., t_{max}) will be reported with the same precision as the actual elapsed sampling time value of the source data.

For the reporting of descriptive statistics for PK data, the mean, geometric mean, median, SD and CIs will be presented to 1 digit more precision. The minimum and maximum will be presented to the same precision. Coefficient of variation (CV%) and geometric CV(%) will always be reported to 1 decimal place.

12.2 Pooling

This is a non-randomized open-label, active-treatment clinical study. Data from all sites and countries will be pooled for analysis, unless otherwise specified for an endpoint or analysis.

12.3 Handling of Covariates

In cases where an analysis of covariance (ANCOVA) model may be used, the only planned covariate is the subject's baseline value on the assessment to be analyzed.

12.4 Definitions

12.4.1 Enrollment

A subject is considered as enrolled after providing informed consent. After a subject has been enrolled, the clinical study protocol applies to that subject. Screening procedures can ONLY be performed on enrolled subjects (i.e., those who have provided informed consent); and thus, enrollment is NOT part of screening.

12.4.2 Baseline

The baseline ABR is the ABR during the historical observation period. Baseline for all other efficacy measures is defined as the last observed value for the efficacy assessment prior to taking the first dose of IP (based on dates or date/times).

For quantitative measurements where change from baseline (CFB) is presented, CFB will be derived as:

$$CFB = (Value\ at\ Timepoint\ X) - (Value\ at\ Baseline)$$

12.4.3 Treatment-Emergence

Non-treatment-emergent (NTE) events, outcomes, or results are those which occur on or after the date of informed consent and prior to administration of the first dose of study medication.

Treatment-emergent (TE) events, outcomes, or results are those which occur on or after the date and time of administration of the first dose of study medication.

12.4.4 Reference Start Date and Study Days

The reference start date for presentation of study days in data listings will be the first date of IP administration in the current study and will be referred to as Day 1.

If the event date is prior to the reference start date the study day will be derived as:

Study Day = (Date of Event) - (Reference Start Date).

If the event date is on or after the reference start date the study day will be derived as:

Study Day = (Date of Event) - (Reference Start Date) + 1.

[Note: Day 0 is not a valid label and should not appear in any dataset.]

12.4.5 Observation Periods

The duration of the historical observation period for historical bleeding episodes in days will be 365 days prior to the first dose of the IP.

The duration of the on-treatment observation period for efficacy (OPE) in days will be calculated as (date of termination – date of first dose + 1).

The duration of any other observation interval in days will be calculated as (date of last day of interval – date of first day of specified interval +1).

Conversion from days to other units of time (weeks, months, or years) will be made to support analyses as needed, using the following formulae:

- Duration in weeks = duration (days) / 7
- Duration in months = 12 x duration (days) /365.2425
- Duration in years = duration (days) /365.2425.

The individual subject durations will be rounded to a scientifically meaningful level of precision after the time unit conversion and before summarization; specifically, the duration will be rounded to the closest whole week, 1/10 of a month, or 1/100 of a year.

12.4.6 Analysis Visit Windows

This study is not expected to require any analysis visit windows. However, an unscheduled visit has been added to the protocol which may occur after the Month 12 visit, in which case it may be mapped to an "End of Study" visit.

12.5 Derived Efficacy Endpoints

12.5.1 Menstrual Bleeding

In the eCRF, the causes of bleeding episodes are recorded differently for the two study periods.

- Historical: Spontaneous, Traumatic, Surgery, Unknown, Other (specify)
- On-Study: Spontaneous, Injury, Surgical, Menstrual bleeding, Unknown.

Prior to performing any other derivations or analyses related to bleeding episodes, the causes of the historical bleeding episodes will be remapped to achieve consistency between the two periods, as shown below:

Cause of Historical Bleeding Episode	**Remapped to:**
Spontaneous	Spontaneous
Traumatic	Injury
Surgery	Surgical
Other (specify), where subject gender is female and the associated free-text field contains any of ['monthly', 'menstrual', 'menstruation', 'menorrhag', <other data-driven	Menstrual bleeding or Spontaneous (if confirmed to be heavy

variations>]. Note: Cases should be reviewed by medical at the time of remapping.	menstrual bleeds/menorrhagia)
Other (specify), where subject gender is not female or the associated free text field does not contain any of ['monthly', 'menstrual', 'menstruation', 'menorrhag', <other data-driven variations>]	To be investigated for possible re-assignment to an established category
Unknown	Unknown

Regular menstrual bleeding was not intended to be captured on the eCRF. Investigators received instructions in the eCRF Completion Guidelines regarding when to record and how to evaluate menorrhagia (incorporating input from the subject).

12.5.2 Annualized Bleeding Rate (ABR)

The annualized bleeding rate (ABR) for each subject will be derived as

$$ABR = \frac{Number\ of\ Bleeding\ Episodes}{Observation\ Period\ [years]}$$

for any observation period. The derivation of the observation periods is described in Section 12.4.5.

ABRs will be calculated overall and by type of bleeding episode (spontaneous, traumatic, surgical, etc.). A spontaneous ABR will be derived separately for each bleed location. Bleeds of unknown cause will be classified as spontaneous bleeds.

12.5.3 Categorized Spontaneous ABR

The ABR for treated spontaneous BEs should be categorized as 0, 1-2, 3-5, or >5. It has been clarified that the intent of this protocol-specified analysis was to capture the number of spontaneous bleeding events that occurred during the study.

12.5.4 ABR Percent Reduction in On-Demand Subjects

The percent reduction in the ABR for treated spontaneous BEs in on-demand subjects will be calculated as 100 x (post-baseline ABR – baseline ABR) / baseline ABR. A subject will be counted as having a clinically meaningful percent reduction of ABR for treated spontaneous BEs if the calculated value is ≤ -25%. If the calculated value is > -25%, then the subject did not experience a clinically meaningful reduction from baseline.

12.5.5 ABR Preservation Success in pdVWF Switch Subjects

ABR preservation success in pdVWF switch subjects is defined using the ABR for treated spontaneous BEs. Preservation success is achieved if the (post-baseline ABR – baseline ABR) ≤ 0 and not achieved if (post-baseline ABR – baseline ABR) > 0.

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12.5.7 [redacted]

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[redacted]

[redacted]

[redacted]

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[redacted]

12.6 Repeated or Unscheduled Assessments of Safety Parameters

If a subject has unplanned, repeated assessments on any day, then the final completed assessment from that day will be selected for descriptive statistics by timepoint.

Unscheduled assessments (i.e., not done at a planned visit) will not be used for time point specific summaries but will be used in tabulation of abnormalities or toxicities.

All assessments will be presented in the data listings.

12.7 Handling of Missing, Unused, and Spurious Data

Imputation of missing safety data will include:

- Missing or incomplete infusion data will be imputed (Section 12.7.1)
- Missing or incomplete start and stop dates for prior/concomitant medications and non-drug therapies will be imputed to support determination of prior and concomitant medication status (Section 12.7.2)
- Missing or incomplete AE start/stop dates, seriousness, severity and relationship to study medication will be imputed (Section 12.7.3, Section 12.7.4, Section 12.7.5, Section 12.7.6, respectively)

- Handling of clinical laboratory values that contain non-numeric values due to assay results that were above or below the limit of quantitation (Section 12.7.7)

Data will not be imputed in any quantitative summaries by timepoint or visit.

Both scheduled and unscheduled assessments will be used in all event-based analyses (occurrence of clinically significant and/or treatment-emergent abnormalities of any type, AEs, etc.). Unscheduled visit data will not be used in any "by-visit" descriptive summaries.

Data such as (but not limited to) laboratory tests that were not specified for collection in the protocol will be reviewed on a case-by-case basis for handling decisions during the study. Full documentation of data related to subject safety will be the primary consideration in establishing how such data will be handled.

Data points which appear to be spurious (e.g., outliers, values incompatible with life) will be queried and either corrected or explained, if possible. Outliers will not be excluded from, or identified in, any analysis unless otherwise specified. Any data points that are specified for exclusion will be documented in table footnotes or cross-referenced to an appropriate listing.

12.7.1 Missing Date of IP

If a subject has a missing or partial date of first administration of study medication in the infusion e-diary, then the first dose date will be imputed as the earliest dispensing date of study drug (from the *Study Drug Administration Diary eCRF*). When applicable, the imputed first dose date will be used for deriving study days, treatment emergence, prior/concomitant status and time to event endpoints.

When the date of the last dose of IP is missing for a subject in the SAF, all efforts will be made to obtain the date from the investigator. If it is still missing after all efforts, then the date of last dose will be imputed as the date of the last visit when IP was returned. The imputed date will be used to calculate treatment duration.

If required for an analysis, any other missing or incomplete date of IP administration will be imputed as the date closest to the planned administration date which is consistent with the available data.

12.7.2 Missing Date Information for Prior/Concomitant Medications, Non-Drug Therapies, and Procedures

For prior or concomitant medications and/or non-drug therapies/procedures, incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

12.7.2.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

12.7.2.1.1 Missing Day, Month, and Year

The start date will be imputed as the date of first dose of IP in the current study.

12.7.2.1.2 Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of IP, then the day and month of the date of the first dose of IP will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the date of the first dose of IP, then 31 December will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the date of the first dose of IP, then 01 January will be assigned to the missing fields

12.7.2.1.3 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure

12.7.2.1.4 Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of IP, then the day of the date of the first dose of IP will be assigned to the missing day

- If either the year is before the year of the date of the first dose of IP, or if both years are the same but the month is before the month of the date of the first dose of IP,

then the last day of the month will be assigned to the missing day

- If either the year is after the year of the date of the first dose of IP, or if both years are the same but the month is after the month of the date of the first dose of IP, then the first day of the month will be assigned to the missing day

12.7.2.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of IP is missing, then replace it with the last visit date. If the imputed stop date is before the (imputed or actual) start date, then the imputed stop date will be equal to the start date.

12.7.2.2.1 Missing Day, Month, and Year

- The end date will be interpreted as "ongoing" and no date will be imputed

12.7.2.2.2 Missing Day and Month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of IP, then the day and month of the date of the last dose of IP will be assigned to the missing fields

- If the year of the incomplete stop date is before the year of the date of the last dose of IP, then 31 December will be assigned to the missing fields

- If the year of the incomplete stop date is after the year of the date of the last dose of IP, then 01 January will be assigned to the missing fields

12.7.2.2.3 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure

12.7.2.2.4 Missing Day Only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of IP, then the day of the date of the last dose of IP will be assigned to the missing day

- If either the year is before the year of the date of the last dose of IP, or if both years are the same but the month is before the month of the date of the last dose of IP,

then the last day of the month will be assigned to the missing day

- If either the year is after the year of the last dose of IP, or if both years are the same but the month is after the month of the date of the last dose of IP, then the first day of the month will be assigned to the missing day

12.7.3 Missing Date Information for Adverse Events

For AEs with partial start dates, the non-missing date parts and the investigator's report regarding the relationship of AE onset to treatment with rVWF or ADVATE will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts, then the AE will be classified as treatment-emergent.

For AEs with partial end dates, no imputation will be made, and no duration will be calculated.

AEs with completely missing start dates will be considered TE, and AEs with completely missing stop dates will be considered ongoing.

12.7.3.1 Incomplete Start Date

Follow the same rules as in Section 12.7.2.1.

12.7.3.2 Incomplete Stop Date

Follow the same rules as in Section 12.7.2.2.

12.7.4 Missing Seriousness

Events of unknown seriousness will be tabulated as SAE's in the final analysis; however, every effort will be made to avoid data lock with events for which a determination of seriousness remains missing. The Medical Monitoring Plan presents details of how this effort will be executed.

12.7.5 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of IP, then a severity of "Mild" will be assumed. If the severity is missing for an AE starting on or after the date of the first dose of IP, then a severity will be assigned as follows.

- If a subject experiences more than one AE categorized under the same preferred term, where one of them is categorized as "severe" and one of them is categorized

as "unknown", then the maximum severity for this preferred term should be counted as "severe" for this subject

- If a subject experiences more than one AE categorized under the same preferred term, one of them is categorized as "mild" or "moderate" and one of them is categorized as "unknown", then the maximum severity for this preferred term should be counted as "unknown" for this subject

The imputed values for severity assessment will be used for incidence summaries, while both the actual and the imputed values will be used in data listings.

12.7.6 Missing Relationship to IP for Adverse Events

If the relationship to IP is missing for an AE starting on or after the date of the first dose of IP, a causality of "Related" will be assigned. The imputed values for relationship to IP will be used for incidence summaries, while both the actual and the imputed values will be presented in data listings.

12.7.7 Character Values of Clinical Laboratory Variables

Laboratory measurements will be presented in SI units, unless otherwise specified for an analysis. If a laboratory result is expected to have a numeric value, but the data which are received include a special character such as ">" or "<", then the result will be assumed to lie outside the range of quantitation.

Any non-PK quantitative laboratory measurement reported as "<X", i.e., below the limit of quantification (BLQ), or ">X", i.e., above the upper limit of quantification will be presented as recorded, i.e., as "<X" or ">X" in listings. All safety laboratory results recorded as "<X" or ">X" will be summarized using the numerical part of the value ("X").

13. ANALYSIS SOFTWARE

Statistical analyses will be performed using Version 9.4 of SAS® and Phoenix® WinNonlin® Version 8.0.

14. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

- The protocol specified that the spontaneous ABR should be categorized as 0, 1-2, 3-5, or >5 bleeding episodesHowever, annualized and average weekly rates may not be integers. Therefore, the ABRs will be categorized as 0, >0 through 2, >2 through 5, >5 events per year.

- The MFAS was added to perform supplementary analyses excluding those subjects with data identified to be removed due to lack of proper ALCOAC source. Planned analyses pertaining to subject disposition, demographics, baseline characteristics, exposure/compliance to IP, and primary and secondary efficacy endpoints will be repeated with the MFAS.

15. REFERENCES

Baxalta Clinical Study Protocol 071301: A Prospective, Phase 3, Open-Label, International Multicenter Study on Efficacy and Safety of Prophylaxis with rVWF in Severe Von Willebrand Disease. Protocol Amendment 6 dated 2018 MAR 12.

Baxalta Clinical Study Protocol 071301: Data Monitoring Committee (DMC) Charter. Final version, dated 2017 FEB 08

European Medicines Agency (EMA) Committee for Medicinal Products for Human Use. Guideline on clinical investigation of human plasma derived von Willebrand factor products. CPMP/BPWG/220/02, 12. 11-17-2005: London, European Medicines Agency (EMA). Web Link: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500067126.pdf

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Shire Standards TFL Library version 9.0 (3.0). (30 MAR 2018).

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16. APPENDICES

16.1 Sample SAS code

16.1.1 Primary Analysis of ABR: Negative Binomial Model

The following SAS® code or an equivalent may be used to perform the primary analysis (Section 6.1):

```
PROC SORT DATA = <ds>;
        BY <subject group> <period> <usubjid>;
RUN;

PROC GLIMMIX DATA = <ds> METHOD = QUAD ORDER = DATA;
        BY <subject group>;
        CLASS <period> <usubjid>;
        MODEL <bleeds> = <period> / DIST = NEGBINOMIAL
                LINK = LOG OFFSET = <logyrs> CL S COVB;
        RANDOM INT / SUB = <usubjid> S CL;
        LSMEANS <period> / CL ILINK;
        LSMESTIMATE <period> -1 1 / CL EXP;
RUN;
```

where <ds> refers to the input dataset, <bleeds> is the number of bleeds during the observation period, <period> is either (1) historical (baseline) or (2) OPE, <age> is the subject's age at baseline, <usubjid> is the unique subject identifier and <logyrs> is the logarithm of the duration of the observation period in years.

16.1.2 Clopper-Pearson CIs

The following SAS® code or an equivalent may be used to obtain Clopper-Pearson CIs:

```
PROC FREQ DATA = <ds>;
    WEIGHT <count>;
    TABLES <result> / binomial (exact cp) cl;
RUN;
```

where <ds> refers to the input dataset, <count> is the number of subjects in the specific response category and <result> is the binomial response value, i.e., "Yes" vs. "No".

16.1.3 Mixed Linear Model for PK Parameter Comparisons

The following SAS® code or an equivalent may be used for comparisons of the PK parameters $AUC_{0\text{-}tau,ss}$, $C_{max,ss}$, and $C_{min,ss}$ as described in Section 8.4:

```
PROC SORT DATA = <ds>;
        BY <subject group> <period> <usubjid>;
RUN;

PROC GLIMMIX DATA = <ds> METHOD = QUAD ORDER = DATA;
        CLASS <period> <usubjid>;
        MODEL <pk parameter> = <period> / DIST = LOGNORMAL LINK =
        LOG CL S COVB;
        RANDOM INT / SUB = <usubjid> S CL;
        LSMEANS <period> / CL ILINK;
        LSMESTIMATE <period> -1 1 / CL EXP;
RUN;
```

where <ds> refers to the input dataset, <pk parameter> is $AUC_{0\text{-}tau,ss}$, $C_{max,ss}$, or $C_{min,ss}$, <period> is either (1) first steady state PK assessment or (2) end of study PK assessment, and <usubjid> is the unique subject identifier.

16.1.4 Median Difference and Hodges-Lehmann CI of Median Difference for Paired Groups

A median and range (minimum, maximum) for $T_{max;ss}$, at the first and second pharmacokinetic assessments, as well as a point estimate and Hodges-Lehmann CI for the log-scale difference (i.e., ratio) of the two assessments, will be generated. Han (2008) provided an explanation of the process and sample SAS code for performing the analysis either in a macro or non-macro code environment. The code and key explanatory points are reproduced below.

16.1.4.1 Statistical Process

1. Obtaining a Point Estimate of the Median difference

    a. Assume that the data consist of N paired observations (x1, y1), (x2, y2), … (xN, yN), where X and Y are correlated random variables, usually through a matched-pair design, for example, crossover designs. Define the random variable D = X - Y and let di = xi - yi, i=1, 2,…, N, denote the N observed differences.

b. Form all possible ordered pairs of differences (di, dj) with i ≤ j. There are N(N + 1)/2 such ordered pairs.

c. For each of the above ordered pairs, compute the average value (di+ dj) /2.

d. The point estimate of the median difference can be obtained by med i≤j [(di + dj) /2].

2. Confidence Interval for the Median Difference

a. Let [λ*, λ*] be the exact 100 x (1-α) % confidence interval for the median difference. Let M = N(N+1) /2 and let A[1] ≤ A[2] ≤… ≤A[M] be the M averages, (di + dj) /2 for all i ≤ j, sorted in ascending order. λ* and λ* can be obtained based on the Wilcoxon Signed-Rank distribution. An asymptotic confidence interval can be computed by applying the normal approximation to the Wilcoxon Signed-Rank distribution. For example, to obtain the lower confidence bound λ*, we use the following procedure.

b. Find t* such that Φ [24 N(N 1)(2N 1) 4t * - N(N 1) + ++] = α /2,

c. Set λ* = A[i], where i = 1 + $\lfloor t^* \rfloor$, and $\lfloor t^* \rfloor$ rounds t* down to the nearest integer.

d. To obtain the upper confidence bound λ*, a complimentary procedure is used.

e. Find t*such that 1- Φ [24N(N 1)(2N 1)4t * - N(N 1)+ ++] = α /2

f. Set λ* = A[i], where i = $\lceil t^* \rceil$, and $\lceil t^* \rceil$ rounds up to the nearest integer.

16.1.4.2 Step-By-Step SAS Code

1. Data step

It is assumed that the data are contained in one data set and are structured as two observations for each subject from the two corresponding treatments, say, treatA and treatB. So, in the code below, we use data DSN as an example, which has three variables, *subject*, *treatA*, *treatB*, where *treatA* and *treatB* are the response from the two treatments. If the data, let's call it TEMP, has three variables as *subject*, *treat*, and *response*, with *treat* has two values "A" and "B". We can use the following code to obtain a data similar to DSN.

```
data temp1(rename=(response=treatA));
set temp;
if treat="A";
run;

data temp2(rename=(response=treatB));
set temp;
if treat="B";
run;

data DSN; merge temp1 temp2;
drop treat;
run;
```

The first step is to calculate the differences between the two groups for each subject and record the sample size as a macro variable for later use.

```
data one; set dsn;
call sumput('size', trim(left(_N_)));
diff=treatA-treatB;
run;
```


2. Using ARRAY to form all possible ordered pairs of differences and average values.
The next step is to form all possible ordered pairs of differences and their average values. We can first transform the data then use ARRAY statement as described below:

```
proc transpose data=one out=two(drop=_name_);
var diff;
run;
```

```
data three;
set two;
array x{&size} col1-col&size;
do i=1 to &size;
do j= i to &size;
stat=(x{i}+x{j})/2;
output;
end;
end;
run;
```

3. Calculate the point estimate of the Hodges-Lehmann median difference

```
proc sort data=three;
by stat;
run;

proc means median noprint;
var stat;
output out=est(drop=_freq_ _type_) median=estimate;
run;
```


4. Calculate the confidence interval of the Hodges-Lehmann median difference

```
data four;
loword=1+int(&size*(&size+1)/4+probit(&alpha/2)*
sqrt(&size*(&size+1)*(2*&size+1)/24));
uppord= ceil( &size*(&size+1)/4+probit(1-&alpha/2)
*sqrt(&size*(&size+1)*(2*&size+1)/24 ));
run;
```

```
data five;
set three end=last;
if _N_=1 then set four;
retain lower upper;
if _N_=loword then lower=stat;
if _N_=uppord then upper=stat;
if last then output;
keep lower upper;
run;
```

5. Put the point estimate and CI into one dataset

```
data HL_est;
merge est five;
run;
```


16.1.4.3 SAS Macro Code

SAS Macro to calculate the point estimate and confidence interval of the Hodges-Lehmann median (paired):

Assume data DSN has three variables: *subject, treatA*, and *treatB*, where *treatA* and *treatB* are the response for the two treatments.

```
%macro HL_paired(dsn=, trt1=, trt2=, alpha=);
data one; set &dsn;
call symput('size',trim(left(_N_)));
diff=&trt1-&trt2;
run;

proc transpose data=one out=two(drop=_name_);
var diff;
run;

data three; set two;
array x{&size} col1-col&size;
do i=1 to &size;
do j= i to &size;
```

```
stat=(x{i}+x{j})/2;
output;
end;
end;

proc sort data=three;
by stat;
run;

proc means median noprint;
var stat;
output out=est(drop=_freq_ _type_) median=estimate;
run;

data four;
loword=1+int(&size*(&size+1)/4 + probit(&alpha/2)
*sqrt(&size*(&size+1)*(2*&size+1)/24));
uppord= ceil(&size*(&size+1)/4 + probit(1-&alpha/2)
*sqrt(&size*(&size+1)*(2*&size+1)/24));
run;

data five; set three end=last;
if _N_=1 then set four;
retain lower upper;
if _N_=loword then lower=stat;
if _N_=uppord then upper=stat;
if last then output;
keep lower upper;
run;

data HL_est; merge est five;
run;

%mend HL_paired;
```

16.2 [redacted]

[redacted]

[redacted]