CLINICAL STUDY PROTOCOL

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

Protocol Version and Date:

Original Protocol: 19 Feb 2014

Amendment 1: 08 Apr 2016

Amendment 2: 15 Dec 2016

Amendment 3: 03 Aug 2017

Amendment 6: 12 Mar 2018

CLINICAL STUDY PROTOCOL

PRODUCT: Recombinant Von Willebrand Factor (rVWF)

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 SHORT TITLE: rVWF IN PROPHYLAXIS

PROTOCOL IDENTIFIER: 071301

CLINICAL TRIAL PHASE 3

ORIGINAL: 2014 FEB 19

OTHER ID(s)
NCT Number: to be determined
EudraCT Number: to be determined
IND NUMBER: to be determined

Study Sponsor(s):	**Baxter Healthcare Corporation**	**Baxter Innovations GmbH**
	One Baxter Way	Industriestrasse 67
	Westlake Village, CA 91362	A-1221 Vienna, AUSTRIA

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted], Global Clinical Development
Baxter Healthcare Corporation

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (e.g. investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) to the ECs.

ALL SAEs ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT

See SAER form for contact information.
Further details are also available in the study team roster.

For definitions and information on the assessment of these events refer to the following:

- AE, Section 12.1
- SAE, Section 12.1.1.1
- Assessment of AEs, Section 12.1.2.

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	Recombinant von Willebrand factor (rVWF)
Name(s) of Active Ingredient(s)	Recombinant von Willebrand factor (rVWF)
CLINICAL CONDITION(S)/INDICATION(S)	
Subjects with severe von Willebrand disease (VWD) requiring prophylactic treatment with coagulation factor replacement	
PROTOCOL ID	071301
PROTOCOL TITLE	A PROSPECTIVE, PHASE 3, OPEN LABEL, INTERNATIONAL MULTICENTER STUDY ON EFFICACY AND SAFETY OF PROPHYLAXIS WITH rVWF IN SEVERE VON WILLEBRAND DISEASE
Short Title	rVWF IN PROPHYLAXIS
STUDY PHASE	Ph3
PLANNED STUDY PERIOD	
Initiation	2014 DEC
Primary Completion	2016 OCT
Study Completion	2016 OCT
Duration	22 months
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
The purpose of this phase 3 study is to investigate the efficacy and safety, including immunogenicity and thrombogenicity, and [redacted] of prophylactic treatment with rVWF in subjects with severe VWD.	
Primary Objective	
The primary objective of this study is to prospectively evaluate the overall annualized bleeding rate (ABR) for spontaneous bleeding episodes while on prophylactic treatment with rVWF and to retrospectively evaluate the subjects' historical ABR for spontaneous bleeding episodes during on-demand treatment.	
Secondary Objective(s)	
Secondary Objectives are • Additional efficacy assessments of prophylactic treatment, • Safety, • Pharmacokinetics (PK), • Efficacy of the treatment of bleeding episodes	
Exploratory Objective(s)	
[redacted]	
STUDY DESIGN	
Study Type/ Classification/ Discipline	Efficacy and Safety
Control Type	No control
Study Indication Type	Prophylaxis and treatment of bleeding episodes
Intervention model	Single-group

Blinding/Masking	Open-label
Study Design	This is a phase 3, prospective, open-label, non-randomized, international multicenter study evaluating efficacy, safety, including immunogenicity and thrombogenicity, and [redacted] of prophylactic treatment regimen with rVWF for subjects with severe VWD.
Planned Duration of Subject Participation	Approximately 16 months

Primary Outcome Measure

Efficacy

- Prospectively recorded overall ABR for spontaneous bleedings during prophylactic treatment with rVWF and the subjects' historical ABR for spontaneous bleedings during on-demand treatment.

Secondary Outcome Measure(s)

Efficacy

- Number of subjects with reduction of ABR forspontaneous bleeding episodes) during prophylaxis compared to the subjects' own historical control during on-demand treatment
- Number of subjects with 0 bleeds during prophylactic treatment with rVWF
- Number of infusions and total weight adjusted consumption of rVWF and ADVATE (recombinant factor VIII/rFVIII) per month and per year

Safety

- Adverse events (AEs)
- Incidence of thrombotic events
- Incidence of severe allergic reactions (i.e. anaphylaxis)
- Development of inhibitory antibodies to VWF and FVIII
- Development of total binding antibodies to VWF and FVIII
- Development of antibodies to Chinese hamster ovary (CHO) proteins, mouse immunoglobulin G (IgG) and rFurin

Pharmacokinetic

- Incremental recovery (IR), terminal half-life (T1/2), mean residence time (MRT), area under the curve/dose (AUC/dose), area under moment curve/dose (AUMC/dose), volume of distribution at steady state (Vss) and clearance (CL) based on Von Willebrand factor Ristocetin cofactor activity (VWF:RCo), Von Willebrand factor antigen (VWF:Ag), Von Willebrand collagen binding activity (VWF:CB) , INNOVANCE VWF Ac (exploratory assay) and time course (72 hours) of FVIII clotting activity (FVIII:C) levels.

Efficacy of the treatment of bleeding episodes

- Number of infusions of rVWF and ADVATE (rFVIII) per bleeding episode
- Weight-adjusted consumption of rVWF and ADVATE per bleeding episode
- Overall hemostatic efficacy rating at resolution of bleed

Exploratory Outcome Measure(s)

- [redacted]

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**Dosage form**: lyophilized powder and solvent for solution for injection **Dosage frequency**: Prophylactic Treatment The standard prophylactic regimen will consist of BAX 111 (rVWF) infusions administered three times weekly at doses of 50±10 IU/kg rVWF:RCo. Dosage may be individualized within this range based on: • the PK data • type and severity of bleeding episodes the subject has experienced in the past • monitoring of appropriate clinical and laboratory measures. Any further adjustment will have to be agreed with the sponsor in advance. Treatment of Bleeding Episodes: Dosage must be individualized based on the subject's weight, type and severity of bleeding episode and monitoring of appropriate clinical and laboratory measures. In general, an initial dose of 40-60 IU/kg VWF:RCo with 30-45 IU rFVIII [ADVATE]/kg) is recommended (rVWF:rFVIII ratio of 1.3:1: ±0.2). In cases of major bleeding episodes, a dose of up to 80 IU/kg VWF:RCo may be infused. Subsequent doses, if necessary, will be administered with or without ADVATE to maintain VWF:RCo and FVIII levels for as long as deemed necessary by the investigator. **Mode of Administration:** intravenous
SUBJECT SELECTION	
Targeted Accrual	Approximately 15 evaluable subjects with severe VWD
Number of Groups/Arms/Cohorts	Single-group

Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject has a documented diagnosis of severe VWD which :
   a. is confirmed by genetic testing and multimer analysis, documented in patient history or at screening
   b. requires prophylactic replacement treatment with VWF containing concentrate to control bleeding. This includes:
      - subjects already on prophylactic treatment
      - subjects currently on-demand treatment for whom prophylactic treatment is recommended according to standard of care at the center
   c. a minimum of documented 3 spontaneous bleeds requiring VWF treatment within 12 months prior to prophylactic treatment.
2. Availability of records to reliably evaluate type, frequency and treatment of bleeding episodes prior to onset of prophylactic treatment for at least 12 months
3. Subject is ≥ 18 years old at the time of screening.
4. If female of childbearing potential, subject presents with a negative blood/urine pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.
5. Subject is willing and able to comply with the requirements of the protocol

Exclusion Criteria

Subjects who meet ANY of the following criteria are not eligible for this study:

1. The subject has been diagnosed with pseudo VWD or another hereditary or acquired coagulation disorder other than VWD (e.g. qualitative and quantitative platelet disorders or elevated prothrombin time (PT)/ international normalized ratio [INR] >1.4).
2. The subject has a history or presence of a VWF inhibitor at screening.
3. The subject has a history or presence of a FVIII inhibitor with a titer ≥ 0.4 BU (by Nijmegen modified Bethesda assay) or ≥ 0.6 BU (by Bethesda assay).
4. The subject has a known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins.
5. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
6. The subject has a medical history of a thromboembolic event.
7. The subject is HIV positive with an absolute Helper T cell (CD4) count <200/mm3.
8. The subject has been diagnosed with significant liver disease as evidenced by any of the following: serum alanine aminotransferase (ALT) 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).
9. The subject has been diagnosed with renal disease, with a serum creatinine level ≥ 2.5 mg/dL.
10. The subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to signing the informed consent.
11. The subject is pregnant or lactating at the time of enrollment.
12. The subject has participated in another clinical study involving another investigational product (IP) or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
13. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
14. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
15. The subject suffers from a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
16. The subject is in prison or compulsory detention by regulatory and/or juridical order
17. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.

Delay criteria

1. If the subject presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) the screening visit will be postponed until the subject has recovered.

STATISTICAL ANALYSIS

Sample Size Calculation

The determination of the sample size for this study is not based on strict statistical considerations.

Planned Statistical Analysis

Primary Outcome Measure:

The focus of the statistical analysis will be descriptive.

For the prospectively recorded overall annualized bleeding rate (ABR) of spontaneous bleedings during prophylactic treatment as well as for the historical ABR of spontaneous bleedings, means and corresponding 90% two-sided confidence intervals based on the negative binomial distribution will be carried out.

Secondary Outcome Measures:

Efficacy:

For the number of infusions and for the total weight adjusted consumption of rVWF and ADVATE per month and per year, summary statistics will be carried out.

For the number of subjects with reduction of ABR as well as for the number of subjects with 0 bleeds, proportions and corresponding 90% two-sided confidence intervals will be performed.

Efficacy of the Treatment of Bleeding Episodes:

For the number of infusions of rVWF and ADVATE per bleeding episode, for the weight adjusted consumption of rVWF and ADVATE per bleeding episode as well as for the overall hemostatic efficacy rating at resolution of bleed, summary statistics will be carried out.

Pharmacokinetic:

The PK parameters $AUC_{0\text{-}72h}$/Dose, $AUC_{0\text{-}\infty}$/Dose, $AUMC_{0\text{-}\infty}$/Dose, MRT (mean residence time), CL (clearance), IR (incremental recovery), T1/2 (elimination phase half-life), Vss (Volume of distribution at steady state), Cmax (maximum concentration) and Tmax (time to reach the maximum concentration) will be summarized by median and corresponding 90% confidence intervals, mean and corresponding 90% confidence intervals, standard deviation, Q1, Q3, IQR, geometric mean and corresponding 90% confidence intervals.

Descriptive statistics will be used to summarize VWF:RCo levels for each nominal time point on the PK curve.

For all subjects concentration vs. time curves will be prepared.

Safety:

The number of subjects who experienced SAEs and the number of SAEs will be tabulated. In addition, the number of subjects who experienced AEs related to IP and the number of IP-related AEs will be tabulated and subcategorized for thrombotic events, inhibitory and total binding antibodies to VWF and FVIII, antibodies to Chinese hamster ovary (CHO) proteins, antibodies to mouse immunoglobulin G (IgG) and antibodies to rFurin.

A listing of all AEs will be presented by subject identifier, age, sex, preferred term and reported term of the AE, duration, severity, seriousness, action taken, outcome, causality assessment, onset date, stop date and medication or non-drug therapy to treat the AE. An overview table for AEs will be provided, presenting the number of AEs, the number of subjects with AEs and the corresponding percent of subjects in total and by seriousness and relationship to study treatment. An additional summary table will present the total number of (mild, moderate, severe) AEs by system organ class and preferred term with relationship to IP.

Exploratory Outcome Measures:

[redacted]

4. TABLE OF CONTENTS

Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABR	Annualized bleeding rate
ADAMTS13	A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, number 13
AE	Adverse event
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC0-∞	Area under the plasma concentration /time curve from time 0 to infinity
AUC_{0-72h}/Dose	Area under the plasma concentration/time curve from time 0 to 72 hours post-infusion/dose
$AUC_{0-\infty}$/Dose	Area under the plasma concentration/time curve from time 0 to infinity/dose
AUC/Dose	Area under the curve/dose
AUMC	Area under moment curve
$AUMC_{0-\infty}$/Dose	Area under the first moment curve from time 0 to infinity/dose
aPTT	Activated partial thromboplastin time
B19V	Parvovirus B19
BILI	Bilirubin
BP	Blood pressure
BU	Bethesda Unit
BUN	Blood urea nitrogen
BW	Body weight
CAM	Cell adhesion molecule
CB	Collagen binding activity
CBC	Complete blood count
CD4	Helper T cell
CHO	Chinese hamster ovary
Cl	Chloride
CL	Clearance
C_{max}	Maximum plasma concentration
CR	Creatinine
eCRF	Electronic case report form
DMC	Data monitoring committee
DIC	Disseminated intravascular coagulation
DVT	Deep vein thrombosis
EC	Ethics committee
ECG	Electrocardiogram

Abbreviation	Definition
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
FVIII	Factor VIII
FVIII:C	Factor VIII clotting activity
GCP	Good Clinical Practice
GI	Gastrointestinal
Glu	Glucose
GPIb	Glycoprotein Ib
HAMA	Human anti- mouse antibodies
HAV	Hepatitis A virus
HB	Hepatitis B
HBs	Hepatitis B surface
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
[redacted]	[redacted]
HRP	Horseradish peroxidase
IB	Investigator's brochure
ICH	International Conference on Harmonisation
Ig	Immunoglobulin
INR	International normalized ratio
IP	Investigational product
IQR	Interquartil range
IR	Incremental recovery
i.v.	Intravenous
K	Potassium
k.o.	Knock out
LDH	Lactate Dehydrogenase
Na	Sodium
NMC	Non-medical complaint
NOAEL	No observed adverse effect level
MRI	Magnetic resonance imaging

Abbreviation	Definition
MRT	Mean residence time
pdVWF	Plasma derived VWF product
pdVWF/FVIII	Plasma derived VWF product containing fractions of FVIII
PCR	Polymerase Chain Reaction
PEF	Peak expiratory flow
PK	Pharmacokinetic
PKFAS	Pharmacokinetic Full Analysis Set
PKPPAS	Pharmacokinetic Per Protocol Analysis Set
PP	Per protocol
PT	Prothrombin time
Q1, Q3	Quartile
rFVIII	Recombinant factor VIII
rVWF	Recombinant von Willebrand factor
RBC	Red blood cell count
SAE	Serious adverse event
SAER	Serious adverse event report
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
[redacted]	[redacted]
SIC	Subject identification code
sP-selectin	Soluble P-selectin
$T_{1/2}$	Elimination phase half life
TIA	Transient ischemic attack
Tmax	Time to reach the maximum concentration
TTP	Thrombotic thrombocytopenic purpura
ULMW	Ultra-large molecular weight
Vss	Volume of distribution at steady state
[redacted]	[redacted]
VTE	Venous thromboembolism (VTE)
VWD	von Willebrand disease
VWF	Von Willebrand factor
VWF:Ag	Von Willebrand factor antigen
VWF Ac	VWF activity measured INNOVANCE VWF Ac assay
VWF:CB	Von Willebrand Factor collagen binding
VWF:RCo	Von Willebrand factor: Ristocetin cofactor activity
WBC	White blood cell

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

Baxter Healthcare Corporation (hereafter referred to as Baxter or sponsor) has developed a human recombinant von Willebrand Factor (rVWF), which is co-expressed with recombinant factor VIII (rFVIII) in a Chinese hamster ovary (CHO) cell line and separated during the subsequent downstream process. To address concerns regarding the risk of transmission of blood-borne pathogens that may be introduced by human plasma, no exogenously added raw materials of human or animal origin are employed in the cell culture, purification, or formulation of the final container product. The only proteins present in the final container product other than rVWF are trace quantities of murine immunoglobulin (IgG, from the immunoaffinity purification), host cell (i.e., CHO) protein, rFurin (used to further process rVWF). rVWF is intended for the treatment of von Willebrand disease (VWD).

rVWF has been developed under the Baxter internal code BAX111 and is used as investigational product (IP) in this study. rVWF may be used with or without ADVATE (rFVIII) for the treatment of bleeding episodes (see Section 8.7.4.4). See Section 8.7 for further information on the IPs and their usage in this study). A detailed description of rVWF is also provided in the Investigator's Brochure (IB).

6.2 Clinical Condition/Indication

Von Willebrand Factor (VWF) is a large multimeric glycoprotein with a molecular weight that varies from 500 to 20,000 kDa. VWF is normally found in plasma and produced in the alpha-granules of platelets and in endothelial cell organelles known as the Weibel-Palade bodies. VWF mediates platelet adhesion and aggregation at sites of vascular injury, one of the key functions in primary hemostasis. VWF also serves to stabilize coagulation factor VIII (FVIII), where FVIII is an essential cofactor of secondary hemostasis, which leads to fibrin clot formation.[1] Qualitative and/or quantitative deficiencies of VWF lead to a highly variable bleeding diathesis known as VWD, the most common of the hereditary coagulation factor deficiencies. Penetrance of VWD is highly variable, with only a small fraction of mildly affected patients displaying clinical symptoms or a family history of a bleeding diathesis.

The current biochemical-based classification distinguishes disorders arising from partial quantitative (type 1), qualitative (type 2), or virtually complete (type 3) deficiencies of VWF. Up to 70% of VWD patients are diagnosed with type 1 VWD, which may also be associated with minor functional defects in the molecule. In general, patients with type 1 VWD display mild clinical symptoms. Approximately 20 to 30% of VWD patients are diagnosed with type 2 VWD. Type 2 VWD is further divided into 4 subtypes (A, B, N, and M), reflecting distinct classes of functional abnormalities. These defects result in abnormal functional and/or multimeric distribution patterns that facilitate their diagnosis. The bleeding diathesis is usually moderate and primarily affects the mucosal tissues. Type 2N VWD patients are sometimes misdiagnosed as mild hemophilia A. Finally, approximately 1% percent of VWD patients exhibit a total or near total absence of VWF, which is classified as type 3 VWD. The incidence of type 3 VWD is estimated at 0.5-1.0 x 10^6. This type is also associated with a very low FVIII level (typically < 5%) because the VWF carrier function for FVIII is lost. Replacement of VWF alone stabilizes endogenous FVIII, resulting in hemostatic levels within several hours post-infusion. Published results from studies of a plasma-derived VWF concentrate demonstrated an increase of FVIII at an approximate rate of 5.8 ±1 IU dL^{-1} h^{-1}.[2] Type 3 VWD patients display severe hemorrhagic symptoms with bleeding predominantly in mucosal tissues, muscle and joints. All VWD patients, particularly those with type 2 or type 3 VWD, are at an increased risk for life-threatening bleeding episodes.

6.3 The role of prophylaxis in the management of VWD

The goals of long term prophylaxis in VWD are to maintain VWF and FVIII at sufficient levels to reduce the frequency and duration of bleeding episodes, the need for red blood cell transfusions, and the risk of complications, such as arthropathy.[3] In contrast to hemophilia, routine prophylaxis is not as established in VWD, although prophylaxis for patients with severe VWD have already been in use in Sweden during the 1950s [4]. In those early days of VWD treatment plasma FVIII concentrates containing VWF fractions were applied for replacement therapy, which then were followed by plasma derived VWF products containing fractions of FVIII (pdVWF/FVIII).

A Swedish cohort including 37 patients with type 3 VWD under prophylactic median treatment of 11 years (range 2 to 45 years) was retrospectively analyzed [5;6]. The doses used for prophylaxis, given once weekly for at least 45 weeks per year, were calculated based on 12 to 50 IU/kg body weight (BW) of factor VIII clotting activity (FVIII:C) which approximately corresponded to 24-100 IU/kg von Willebrand factor: Ristocetin cofactor activity (VWF:RCo) considering that mainly Haemate with a known VWF:RCo/FVIII:C ratio of about 2 was used. An escalation of doses from one to three dose levels was allowed depending on the frequency and severity of bleedings.

The results demonstrate that under long-term prophylaxis the number of bleeds could be reduced dramatically. Whereas the median value for bleeds per year was about 10 before prophylaxis this value could be reduced to less than 1 bleed per year during prophylaxis.

The benefit of prophylaxis for such indications was retrospectively also demonstrated in a cohort of Italian patients including type 3, 2A, 2M and type 1 patients. Prophylaxis was started after severe gastrointestinal or joint bleedings and completely prevented bleedings in 8 of these 11 patients and largely reduced the need of blood transfusions in the remaining three. A regimen of 40 IU rVWF:RCo/kg was applied every other day or twice a week. A prospective study on prophylaxis, the PRO.WILL study, has been initiated in Italy [7].

The results of a prospective study investigating the prophylaxis in children and young adults showed a significantly reduced bleeding frequency and bleeding score (3 vs. 0.07; 3 vs. 0. p<0.001) compared to the pre-prophylaxis values. The median dose was 40 (20-47) IU/kg VWF:RCo administered mainly twice weekly in 23 patients, three times a week in 7 patients and four times a week in 2 children [8].

The VWD Prophylaxis Network initiated the VWD International Prophylaxis (VIP) trial to investigate the role of prophylaxis in patients with severe VWD including Type 1, 2 and 3. The dose of the factor replacement product was 50 IU /kgVWF:RCo. The frequency of the dose depended on the type of bleeding and could be increased from once weekly to twice weekly or three times per week. For the treatment of menorrhagia the dose of 50 IU/kg VWF:RCo was given on the first day of menses for 2 cycles. The frequency could be increased to day 1 and 2 for 2 cycles or to day 1, 2, and 3 of menses.

The study contains both retrospective and prospective study components. Results from the retrospective study component were published, including sixty-one subjects on prophylactic regimen in the past 6 months prior to enrollment or subjects with a history of prophylaxis over at least 6 month [9]. Differences in annualized bleeding rates (ABR) within individuals (during prophylaxis – before prophylaxis) were significant for those with primary indications of epistaxis (P = 0.0005), joint bleeding (P = 0.002) and gastrointestinal (GI) bleeding (P = 0.001). The difference in the group whose primary indication for treatment was abnormally heavy bleeding at menstruation (n = 4) was not significant (P = 0.25). The reduction of mucosal bleeding likely not only dependents on normal circulating levels of active VWF, but also on the presence of discrete concentrations of normal VWF inside the platelets and within endothelial matrices. The low subject number (n=4) and the treatment scheme for menorrhagia on days 1, 2, and 3 of menses which might represent rather on-demand than prophylactic treatment may also account for the outcome in this study.

The results of the VIP study and previous investigations suggest that VWD patients with recurrent bleedings and severe menorrhagia will benefit from a prophylactic VWF replacement therapy. There is evidence that up to 40 % of patients with type 3 VWD experience joint bleeding which can lead to hemophilic arthropathy. Other potential indications for prophylaxis include patients with type 2A or 2B VWD with recurrent gastrointestinal bleeding, menorrhagia or frequent epistaxis [3]. Long-term prophylaxis for most patients with type 3 VWD and in some patients with type 1 or 2 VWD, depending on the pattern of bleeding, may be the treatment option of choice. Although the main experience with long-term prophylaxis is with secondary prophylaxis, primary prophylaxis starting at young age is recommended to prevent arthropathy in patients with severe VWD.[10]

However, further studies are needed to develop evidence-based guidelines for prophylactic treatment in VWD.

6.4 Population to be Studied

A total of approximately 18 eligible, adult subjects to achieve approximately 15 evaluable subjects with severe VWD are planned to be enrolled, of which a subset of at least 5 subjects will have type 3 VWD. Enrolled subjects (i.e., subjects who have signed the informed consent form) will be eligible to participate in the study if they meet all of the inclusion criteria (see Section 9.1) and none of the exclusion criteria (see Section 9.2).

6.5 Findings from Nonclinical and Clinical Studies

The following summarizes the key findings from relevant nonclinical studies as well as from the completed clinical Phase 1 study **070701** and **071104**. Potential risks and efficacy of rVWF:ADVATE are summarized in the following sections. For additional information on nonclinical and clinical Phase 1 results refer to the rVWF IB.

6.5.1 Findings from Nonclinical Studies

6.5.1.1 Primary Pharmacodynamics

Efficacy of rVWF combined with ADVATE was shown in VWD animal models, which have also low endogenous FVIII levels. Time to occlusion and stable thrombus formation was assessed in the carotid occlusion model in VWD mice. The results demonstrated that rVWF in combination with ADVATE acted efficiently in a dose-dependent manner and had higher efficacy than rVWF alone or plasma derived (pd)VWF. These results were confirmed in an additional study assessing blood loss and survival in a tail tip bleeding model in VWD mice. In a VWD dog rVWF stabilized canine FVIII in the circulation and significantly reduced the bleeding time.

6.5.1.2 Safety Pharmacology

The anaphylactoid and thrombogenic potential of the co-infusion of ADVATE and rVWF and the co-infused product's effects on blood pressure, cardiac and respiratory function and parameters of coagulation activation were investigated in four in vivo studies in different animal models. Safety Pharmacology Studies in rats, guinea pigs, rabbits and dogs revealed no risks for anaphylactoid and thrombogenic potential of ADVATE in combination with rVWF. All observations in safety pharmacology studies are considered to lie within the biological variability of animal models or occurred due to known species-specific anaphylactoid effects of excipients.

6.5.1.3 Pharmacokinetics

Pharmacokinetic studies of both rVWF alone and combined with human rFVIII (rVWF+ADVATE) were conducted in VWD mice, VWD dogs, VWD pigs, rats and cynomolgus monkeys. Human rVWF stabilized the endogenous FVIII in VWD mice, VWD pigs and VWD dogs. Furthermore, the hypotheses that the area under the curve (AUC) with rVWF alone and rVWF+ADVATE is not inferior to the AUC with pdVWF (Haemate P) was tested and confirmed statistically in normal rats. The pharmacokinetic (PK) characteristics of ADVATE were not affected by co-administration of rVWF in cynomolgus monkeys. The PK data in the FVIII knock out (k.o.) mice model are inconclusive and might not be relevant for the clinical situation. However, a stabilizing effect of VWF on FVIII could be shown in a double knock out model in a dose dependent manner.

6.5.1.4 Toxicology

Single dose toxicity studies were conducted in C57BL/6J-mice, VWD mice, rats, rabbits, and cynomolgus monkeys. Rats, rabbits, and cynomolgus monkeys showed no signs of toxicity. Signs of microthrombosis, an exaggerated pharmacological effect, were observed in mice. Mice are not capable of sufficiently cleaving the rVWF subunit as murine disintegrin and metalloproteinase with a thrombospondin type 1 motif, number 13 (ADAMTS13) does not decrease the ultra-large molecular weight multimers of rVWF [11]. The observed symptoms of microthrombosis are interpreted as a species-specific exaggerated pharmacological effect. Studies evaluating the safety of repeated administration of rVWF with or without ADVATE (daily over 14 days) were performed in a rodent (rat) and non-rodent (cynomolgus monkey) species. Reversible signs of exaggerated pharmacological effects (regenerative anemia, thrombocytopenia, and treatment-related histopathologic changes in the heart, liver, and spleen) were observed in rats that were administered 1400 U VWF:RCo/kg /day + 1080 IU ADVATE/kg/day intravenously once daily for 14 days. Also, these findings are interpreted as a species-

specific exaggerated pharmacological effect due to the low susceptibility of human rVWF to cleavage by rodent ADAMTS13 [11]. No toxicologically relevant changes were evident for clinical observations, body weight, feed consumption, ophthalmology, urinalysis, coagulation and serum chemistry parameters, platelet aggregation, and gross pathology. rVWF combined with ADVATE was well tolerated in cynomolgus monkeys after daily intravenous (i.v.) (bolus) administration of 100 U VWF:RCo/kg rVWF combined with 77 IU/kg ADVATE over a period of 14 days. No adverse effects could be detected in this species. There were no signs of hemolysis, thrombosis or thrombocytopenia after repeated intravenous application of rVWF with or without ADVATE. Therefore, 100 U VWF:RCo/kg/day rVWF with or without 77 IU/kg ADVATE was considered the no observed adverse effect level (NOAEL) in this study, which was the highest dose tested. Anti-drug antibodies, however, were formed in both species and resulted in a significant reduction in drug exposure after 14 applications as compared to a single application. These antibodies substantially reduced the systemic exposure to the test substance as compared to a single dose administration. No adverse effects due to antibody formation were observed in both species. rVWF combined with ADVATE was well tolerated locally and no genotoxic potential was evident after two in vitro and one in vivo genotoxicity study. A study on the influence of co-administration of VWF and ADVATE on the immunogenicity of ADVATE in three different hemophilic mouse models (E17 hemophilic Balb/c mice, E17 hemophilic C57BL/6J mice and E17 hemophilic human F8 transgenic mice) showed that rVWF does not negatively impact the immunogenicity of ADVATE in any of the three different hemophilic mouse models.

6.5.2 Findings from Clinical Studies

Two phase 1 studies with rVWF either alone or co-administrated with ADVATE in patients with VWD **070701** and Hemophilia A **071104** have been conducted and the results were analyzed and evaluated. Details on study design, populations enrolled and safety and efficacy outcomes of these two phase 1 studies are presented in Section 6.5.2.1 and Section 6.5.2.2.

Refer to rVWF IB for periodic updates from other rVWF studies.

6.5.2.1 Study 070701

Phase 1 clinical study **070701** was a multicenter, controlled, randomized, single-blind prospective 3-step, dose escalation study to investigate safety, tolerability and PK of rVWF combined at a fixed ratio with ADVATE (VWF:RCo/FVIII:C of 1.3 ± 0.2:1) in adults with severe VWD. Subjects were enrolled in sequential cohorts in a dose escalating manner: Cohort 1, 2 and 3 received a single intravenous infusion of rVWF:ADVATE at the following doses: 2 IU/kg VWF:RCo (Cohort 1), 7.5 IU/kg VWF:RCo (Cohort 2), and 20 IU/kg VWF:RCo (Cohort 3). Subjects in Cohort 4 received a single intravenous infusion of rVWF:ADVATE and pdVWF/ADVATE at 50 IU/kg VWF:RCo in random order.

The primary endpoint was the tolerability and safety after single dose injections of rVWF:ADVATE at 2, 7.5, 20 and 50 IU/kg VWF:RCo for up to 30 days after the last IP infusion. The data generated in this phase 1 study suggest that rVWF:ADVATE up to the highest investigated dose of 50 IU/kg VWF:RCo is well tolerated and safe in adults with severe VWD. No thrombogenic risk or TTP-like syndrome was observed, and no inhibitory antibodies to VWF or FVIII were identified. There were no deaths or other serious adverse reactions, and no infusions were interrupted or stopped due to an AE. Overall, the reported AE profile was similar between the recombinant and plasma-derived concentrates.

Secondary endpoints were the PK assessment of VWF:RCo, von Willebrand factor antigen (VWF:Ag) and multimeric composition of rVWF as well as FVIII:C at standardized time points after single injections of rVWF:ADVATE and pdVWF:FVIII.

The median VWF:RCo half-life ($T_{1/2}$) of rVWF at the 50 IU/kg dose was 16 hours. $T_{1/2}$ with pdVWF:FVIII at the same dose level appeared shorter at 12.58 hours, however, the limits of the 90% CI were similar (11.73 to 17.7 hours vs. 11.87 to 18.03 hours). The median half-lives of VWF:RCo were shorter with the lower investigated doses: 7.13 hours and 13.23 hours with the 7.5 IU/kg and 20 IU/kg doses, although these data were derived from a much smaller number of subjects.

In consequence of the missing ADAMTS13 cleavage ultra-large molecular weight (ULMW) multimers are contained in the rVWF final product. The immediate cleavage of these ultra-large multimers by ADAMTS13 upon release into the circulation could be demonstrated applying Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE)/Immunoblot with polyclonal anti-VWF antibodies to detect the resulting rVWF subunit cleavage fragments.

Overall the data generated in this phase 1 study suggest that rVWF:ADVATE is well tolerated and safe in adults with severe VWD.

6.5.2.2 Study 071104

This study was a prospective, uncontrolled, non-randomized, multicenter proof of concept study to assess safety and PK of the addition of rVWF to ADVATE treatment in 12 evaluable subjects with severe hemophilia A. All subjects underwent 3 PK analyses: the first after infusion with ADVATE alone, the second after infusion with ADVATE plus 10 IU/kg rVWF and the third after infusion with ADVATE plus 50 IU/kg rVWF.

The PK analysis was performed at intervals of approximately 8 to 14 days. Before each infusion for PK assessment there was a wash-out period of at least 5 days and the subjects were not actively bleeding.

Primary outcome measures indicate that co-administration of rVWF slightly sustain ADVATE activity with the highest observed ADVATE half-life of 13.74 h (CI 11.44 to 16.52) after co-infusion of 50 IU/kg ADVATE plus 50 IU/kg rVWF:RCo. The highest improvement in ADVATE circulating half-life was observed in subjects with VWF:Ag levels below 100% which indicates an association between baseline VWF:Ag levels and ADVATE half-life increase.

No treatment related adverse events (AEs) or serious adverse events (SAEs) were reported. No subject withdrew due to an AE and there were no deaths. No binding antibodies to VWF, CHO and rFurin were detectable in the confirmatory assay and no signs of a hypersensitivity to rVWF or ADVATE antigen were observed. Laboratory values over time did not indicate any potential safety risk for hemophilia A patients treated with rVWF and ADVATE in combination.

In summary, the data indicate that rVWF co-administered with ADVATE up to the highest dose of 50 IU/kg VWF:RCo is well tolerated and safe in hemophilia A patients.

6.6 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

Current treatment of VWD patients relies on desmopressin and VWF products manufactured from pooled human plasma. Human VWF produced by recombinant technology could offer a new perspective in treatment of VWD. The benefit for the individual subject is anticipated to be significant during this clinical study. He/she may benefit from a product that minimizes excessive FVIII administration. Variations in VWF multimeric composition may lead to variability with respect to treating or preventing bleeds in VWD subjects, especially mucosal bleeds which are especially problematic. rVWF product manufactured by Baxter consistently contains ultra-large molecular weight (ULMW) VWF multimers due to the fact that the product has not been exposed to ADAMTS13. The initial presence of these ULMW VWF multimers, which are subsequently cleaved by the subject's endogenous ADAMTS13, may result in improved platelet and collagen binding and therefore provide more predictable treatment outcomes. By using a recombinant product, the risk of contamination with blood derived viruses or variant Creutzfeldt-Jakob Disease associated with the use of products of human or animal origin has been virtually eliminated. At this stage of product development, the key societal benefit is a better understanding of advanced treatment options for VWD and enhanced product availability.

These benefits outweigh the following potential risks of rVWF:

- allergic type hypersensitivity reactions as with any intravenous protein product
- the occurrence of thrombotic events
- the development of neutralizing antibodies to VWF

Refer to the IB for further details on benefits and risks of the IP.

6.7 Compliance Statement

This study will be conducted in accordance with this protocol, the International Conference on Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the European Clinical Trial Directive (2001/20/EC and 2005/28/EC), and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of this phase 3 study is to investigate the efficacy and safety, including immunogenicity and thrombogenicity, and [redacted] of prophylactic treatment with rVWF in subjects with severe VWD.

7.2 Primary Objective

The primary objective of this study is to prospectively evaluate the overall annualized bleeding rate (ABR) for spontaneous bleeding episodes while on prophylactic treatment with rVWF and to retrospectively evaluate the patients historical ABR for spontaneous bleeding episodes during on-demand treatment.

7.3 Secondary Objectives

Secondary Objectives are:

- Additional efficacy assessments of prophylactic treatment,
- Safety,
- Pharmacokinetics (PK),
- Efficacy of the treatment of bleeding episodes

7.4 Exploratory Objectives

7.4.1 [redacted]

[redacted]

8. STUDY DESIGN

8.1 Brief Summary

8.2 Overall Study Design

This is a prospective, open label, uncontrolled, non-randomized, international, multicenter phase 3 study to evaluate efficacy, safety, including immunogenicity and thrombogenicity and [redacted] of a prophylactic treatment regimen with rVWF in patients with severe VWD.

The dose of rVWF for prophylaxis will be in the range of 50 ±10 IU/kg rVWF:RCo administered 3 times weekly. The dose may be adjusted within this range based on the subject's history of bleeding episodes, the clinical response and the results from clinical and laboratory assessments (see Section 8.7.4.2).

The overall duration of prophylactic treatment per subject will be 12 months.

During this period any bleeding episodes requiring substitution therapy with VWF concentrate to control bleeding will be treated with rVWF with or without ADVATE. The dose will be according to the bleeding severity and it will be adjusted to the clinical response (see Section 10.3.4).

The overall study design is illustrated in Figure 1.

8.3 Duration of Study Period(s) and Subject Participation

The overall duration of the study is approximately 22 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The subject participation period is approximately 16 months from enrollment to completion (i.e, last study visit), unless the subject is prematurely discontinued.

8.4 Outcome Measures

8.4.1 Primary Outcome Measure

The primary outcome measure is

- Efficacy:
  - Prospectively recorded overall ABR for spontaneous bleedings during prophylactic treatment with rVWF and the subjects' historical ABR for spontaneous bleedings during on-demand treatment.

8.4.2 Secondary Outcome Measures

8.4.2.1 Efficacy

- Number of subjects with reduction of ABR for spontaneous bleeding episodes during prophylaxis compared to the subjects' own historical control during on-demand treatment
- Number of subjects with 0 bleeds during prophylactic treatment with rVWF
- Number of infusions and total weight adjusted consumption of rVWF and ADVATE per month and per year

8.4.2.2 Safety

- AEs
- Incidence of thrombotic events
- Incidence of severe allergic reactions (e.g. anaphylaxis)
- Development of inhibitory antibodies to VWF and FVIII
- Development of total binding antibodies to VWF and FVIII
- Development of antibodies to Chinese hamster ovary (CHO) proteins, mouse immunoglobulin G (IgG) and rFurin

8.4.2.3 Pharmacokinetics

- Incremental recovery (IR), terminal half-life ($T_{1/2}$), mean residence time (MRT), area under the curve/dose (AUC/dose), area under moment curve/dose (AUMC/dose), volume of distribution at steady state (Vss) and clearance (CL) based on Von Willebrand factor Ristocetin cofactor activity (VWF:RCo), Von Willebrand factor antigen (VWF:Ag), Von Willebrand collagen binding activity (VWF:CB) , INNOVANCE VWF Ac (exploratory assay) and time course (72 hours) of FVIII clotting activity (FVIII:C) levels.

8.4.2.4 Efficacy of the Treatment of Bleeding Episodes

- Number of infusions of rVWF and ADVATE per bleeding episode
- Weight-adjusted consumption of rVWF and ADVATE per bleeding episode
- Overall hemostatic efficacy rating at resolution of bleed

8.4.3 Exploratory Outcomes Measure

[redacted]

8.5 Randomization and Blinding

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

8.6 Study Stopping Rules

This study will be stopped if 1 or more of the following criteria are met:

1. Two subjects develop a thrombosis, other than superficial thrombosis
2. Two subjects develop anaphylactoid reactions (e.g. hives, generalized urticaria, tightness of the chest, wheezing, hypotension, or anaphylaxis)
3. Two subjects develop signs and symptoms, suggestive of a thrombotic thrombocytopenic purpura-like syndrome (subjects with type 2B VWD developing thrombocytopenia or changes of the platelet count as described below, will be evaluated on case by case, whether they need to be accounted for), such as
    - A drop in platelet count of 50% of subject's baseline or less than 100.000 per microliter
    - 3 fold increase in Lactate dehydrogenase (LDH)
    - Impaired renal function as determined by:
        - Creatinine increase of 1.5 fold from baseline levels
        - Blood urea nitrogen (BUN) increase from normal levels to a level > 60 mg/dL
4. Two subjects develop rVWF inhibitory antibodies

The study may be stopped at any time by the sponsor.

The sponsor ultimately will decide whether to terminate, temporarily halt or modify the study based on the Data monitoring committee (DMC) recommendation.

8.7 Investigational Product(s)

8.7.1 Packaging, Labeling, and Storage

8.7.1.1 rVWF (Recombinant von Willebrand Factor)

rVWF will be packaged in boxes with 2 glass vials, one containing the lyophilized rVWF, and the second vial containing the diluent. Further details are provided in the IB and Pharmacy Manual. The rVWF label will include, at a minimum, the actual VWF:RCo potency and the date of expiration.

rVWF should be refrigerated (2°-8°C [36°-46°F]) in lyophilized form. Deviations from the storage condition have to be communicated and followed up with the sponsor. Inadequately stored product will have to be placed on quarantine and may only be used after written investigational product administration authorization by the sponsor. After removal of the product from the refrigerator the product must not be returned to the refrigerator and has to be used immediately. rVWF must not be used beyond the expiration date printed on the vial. Avoid freezing at all times.

8.7.1.2 rFVIII (Recombinant FactorVIII /ADVATE)

ADVATE will be packaged in boxes with 2 glass vials, one containing the lyophilized rFVIII, and the second vial containing the diluent. Further details are provided in the IB and Pharmacy Manual. The ADVATE label will include, at a minimum, the actual FVIII:C potency and the date of expiration.

ADVATE should be refrigerated (2°-8°C [36°-46°F]) in powder form and should not be used beyond the expiration date printed on the vial. Deviations from the storage condition have to be communicated and followed up with the sponsor. Inadequately stored product will have to be placed on quarantine and may only be used after written investigational product administration authorization by the sponsor. After removal of the product from the refrigerator the product must not be returned to the refrigerator and has to be used immediately. Avoid freezing at all times.

8.7.2 Reconstitution

The reconstitution procedures for both rVWF and ADVATE products are detailed in the Pharmacy Manual.

8.7.3 Administration

Following reconstitution, rVWF and ADVATE (in case of bleeding episode treatment) should be administered to study subjects at room temperature and within 3 hours of reconstitution. The reconstituted rVWF and ADVATE, should be inspected for particulate matter and discoloration prior to administration, whenever the solution and container permit. The solution should be clear and colorless in appearance. If not, do not administer the product. Plastic syringes provided by the sponsor must be used since coagulation factors tend to stick to the surface of glass syringes.

IP infusions should be given at a rate which should not exceed 4 mL/minute. The investigator/ subject shall ensure that no visible residual volume remains in the syringe(s) and that the complete content is administered. Upon completion of the infusion, the butterfly catheter should be flushed with at least 2 mL of saline solution. In case of a (central) venous access device, the flush should be with at least 10 mL of saline solution.

Only the actual potencies of rVWF and ADVATE as stated on the vial labels and described in the Pharmacy Manual should be used. A variation of up to 10% of the intended dose for prophylactic infusions and of the intended dose for treatment of bleeding episodes is permissible and the exact dose should be recorded on the Case Report Form (CRF).

At study visits where recovery analysis is being done, vials with the same lot numbers should be used throughout the PK IP infusion per subject.

For treatment of bleeding episodes there are two options for the preparation of rVWF and ADVATE for infusion if needed.

Preferably sequential administration will be done: separate syringes of the appropriate dose of rVWF and ADVATE will be prepared for sequential infusion. rVWF should be infused first sequentially followed preferably within 10 minutes by infusion of ADVATE. Only the actual potencies of rVWF and ADVATE as stated on the vial labels and described in the Pharmacy Manual should be used.

Alternatively, premixed solutions can be administered: rVWF and ADVATE will be pre-mixed in a single syringe to achieve the appropriate dose. The contents of each vial of rVWF or ADVATE can be drawn into one syringe by using a separate unused reconstitution device as described in the Pharmacy Manual.

The final dose of rVWF:ADVATE should be at a ratio of 1.3:1 ± 0.2.

8.7.4 Description of Treatment

8.7.4.1 Baseline Visit (PK-Assessment Treatment)

The first IP infusion for PK assessment should be within 60 days after the completion of screening procedures and confirmation of eligibility.

At the baseline visit the subjects will receive a dose of 50± 5IU/kg rVWF:RCo for PK assessment. Blood samples will be drawn within 30 minutes pre-infusion, and at 7 time points post-infusion (30±5 minutes, 60± 5 minutes, 6±1 hours, 12 ± 1 hours, 24± 2 hours, 48± 2 hours, 72± 2 hours).

If a subject is already on a prophylactic treatment scheme using a pdVWF a washout period of at least 5 days is required prior to infusion of rVWF for PK assessment.

Subjects previously enrolled in rVWF studies **070701** or **071001** and having previously undergone PK assessments in these studies are required to repeat the PK assessment due to different dose and time points used in these former studies (see Section 12.9.1 and , Section 20.3 A washout period of at least 5 days is required prior to infusion of rVWF for PK assessment for subjects previously treated with rVWF.

Subjects who participated in the surgery study **071101** will not need an additional PK assessment if they transfer to this study. Identical PK dose and time points are used for both studies **071101** and **071301**.

8.7.4.2 Prophylaxis Initiation Treatment

The prophylaxis initiation treatment visit will coincide with the 72±2 h PK assessment. At this visit subjects will receive their prophylaxis initiation dose of 50 ± 10 IU/kg rVWF:RCo after the blood draw for the 72±2 hours post-infusion PK assessment. If subjects do not need an additional PK assessment (e.g. subject has transferred from the surgery study **071101**), subjects must receive the IP for prophylaxis initiation treatment within 60 days after screening and confirmation of eligibility. The exact standard prophylaxis dose may range between 40 and 60 IU/kg based on:

- available historical PK data
- type and severity of bleeding episodes the subject has experienced in the past and
- monitoring of appropriate clinical and laboratory measures.

Dose adjustments during the continued prophylactic treatment are described in Section 8.7.4.3.

The subject will be trained on IP reconstitution and administration and may then qualify for home treatment (see Section 8.7.4.3.1). Refer to Table 4 for study procedures and Table 5 for clinical laboratory assessments.

8.7.4.3 Prophylaxis Treatment

The standard prophylaxis is an infusion of 50 ±10 IU/kg rVWF:RCo administered three times per week. Examples of possible dosing schedule are given in Table 1.

Table 1.
rVWF Dosing Schedule Examples: Schedules 1 and 2

Example	Mon	Tues	Wed	Thurs	Fri	Sat	Sun
Schedule 1	X		X		X		
Schedule 2		X		X		X	

Any further dose and frequency adjustment will be agreed with the sponsor in advance unless it constitutes an urgent safety measure. Dose adjustments to higher doses (not exceeding the upper dose limit of 80 IU/kg rVWF:RCo) and adjustments to 4 times weekly administration will only be allowed in cases of persisting high bleeding rates due to insufficient therapeutic response.

Dose and frequency reduction will only be allowed in case plasma VWF or FVIII levels are exceeding the recommended ranges.

If a subject does not adequately respond to rVWF therapy, he/she will be evaluated for the presence of inhibitory and total binding anti-VWF antibodies (see Section 12.9.3.2).

It is essential for the success of this study that the subjects adhere to treatment regimens. Therefore, procedures for monitoring subject's compliance are implemented (see Section 10.7).

If one infusion of IP is missed, the subject may administer the IP as soon as possible. The subject should then adhere to the standard prophylaxis treatment scheme ensuring a minimum interval of 12 hours between this and the previous IP infusion. For example, a subject routinely infuses IP on Monday, Wednesday and Friday, he/she misses the Wednesday time point and therefore may infuse the IP on the next day (Thursday) and thereafter proceed with infusing the IP on Friday (considering a minimum 12 hours between the infusions) and return to the initially chosen schedule.

If more than 30% of infusions of IP are missed within the visit interval of 3 months the subject will be discontinued from the study (see Section 9.4).

8.7.4.3.1 General Instructions for Home Treatment for Prophylaxis

At the discretion of the investigator, a subject may be considered suitable for home treatment only after the subject has received at least 1 infusion of IP in the clinic, either during planned IP exposure (PK or prophylaxis) or during the treatment of bleeding episodes, and meets the following additional criteria:

1. Fully understands the concept of a clinical study and related documentation (documented training of at least 30 minutes),
2. Has a history of previous experience with home treatment including self-administration and treatment with VWF containing concentrates,
3. Has adequate time for initial training of the study drug preparation (preparation, mixing and infusion of the IP(s) (documented training of at least 30 minutes).

In the event a healthcare professional is required to administer IP, he/she must be trained and qualified by the sponsor on the above procedures prior to the decision for home treatment. A Subject Guideline detailing all instructions and information listed above will be provided to each subject.

8.7.4.4 Treatment of Bleeding Episodes

8.7.4.4.1 General Instructions for Home Treatment of Bleeding Episodes

If a subject experiences a bleeding episode, he/she should contact the study site immediately and the site investigator should provide instructions on the treatment regimen. If the subject initiates the treatment at home, he/she should at least follow up with the study site if a visit is needed as per hospital standard.

In the event a healthcare professional is required to administer treatment at the subject's home, he/she must be trained and qualified by the sponsor on the above procedures prior to the decision for home treatment. Once a subject has received 1 infusion of rVWF in the clinic (either during planned IP exposure or during the treatment of a bleeding episode) and meets the criteria for home treatment, the treatment of bleeding episodes with IP can be conducted at home (see Section 8.7.4.3.1).

If a subject is not qualified for home treatment, rVWF infusions must be administered at the study site.

If a subject experiences a bleeding episode that requires treatment between the screening and the prophylaxis initiation visit, the subject will be treated with IP (rVWF with or without ADVATE). Treatment with IP must occur at the study site unless the subject has previously qualified for home treatment with rVWF. If rVWF treatment is not feasible, the subject may use his/her standard of care, such as commercial pdVWF/FVIII products. In any case a washout period of at least 5 days is required prior to rVWF PK infusion at the PK assessment visit.

If a subject experiences a bleeding episode requiring treatment during the PK assessment, rVWF will be used to treat the bleed. Blood draws for PK assessment will be stopped and the PK assessments will be repeated once the bleed has resolved and the subject is free of any symptoms related with the bleeding episode. Dose and frequency of rVWF infusions or any other replacement therapy to stop the bleed should be recorded in the e-CRF.

8.7.4.4.2 Dosing Recommendations for Treatment of Bleeding Episodes

If an acute bleeding episode occurs, the subject will be treated with rVWF with or without ADVATE. In general initially, an infusion of rVWF: ADVATE at a rVWF: ADVATE ratio of 1.3:1±0.2 will be administered. Subsequent infusions may either use rVWF alone or with ADVATE, based on FVIII levels, if available.

If FVIII levels are not available, dosing is at the discretion of the investigator based upon the individual subject's PK data. Using ADVATE in addition to rVWF in subsequent doses carries the risk of an excessive rise in FVIII:C. Therefore, reduced doses of ADVATE and/or prolongation of the dose interval should be considered.

In general the aim of the initial dose should be full replacement of VWF with VWF:RCo levels of > 0.6 IU/ml (60%) and FVIII:C of > 0.4 IU/mL (40%). In major bleeding episodes, subsequent doses should keep the trough level of VWF:RCo >50% for 3 days and then as deemed necessary by the investigator for subsequent days. In moderate bleeding episodes, the dose and trough level may be reduced to >30% for as long as deemed necessary by the investigator. Treatment for minor bleeding episodes will generally consist of only 1 or 2 doses of rVWF IP.

If the VWF:RCo level is above 150%, a planned treatment should be delayed by at least 12 hours; if the VWF:RCo level is above 200%, a planned treatment should be delayed by at least 24 hours. In either case, a lower subsequent dose (e.g., 20 IU/kg VWF:RCo) may be appropriate.

Dosing recommendations are listed in Table 2.

Dosage must be individualized based on the subject's weight, VWD type and the severity of the bleeding episode, as well as on monitoring of appropriate clinical and laboratory measures. In the phase 1 study **070701**, 1.0 IU/kg VWF:RCo raised the circulating level of VWF:RCo by 0.017 IU/mL (1.7 %). In the same study, the observed mean half-life for rVWF was 19.3 hours, with a standard deviation of 10.9 hours.

Table 2
rVWF:RCo Dosing Recommendations for the Treatment of Bleedings due to VWD

Classification of VWD	**Hemorrhage**	**Dosage (IU VWF:RCo/kg body weight)**
Type 1 • Severe (Baseline VWF:RCo activity typically <20%)	Minor (e.g. epistaxis, oral bleeding, menorrhagia)	40 to 50 IU/kg (1 or 2 doses)
	Major (e.g. severe or refractory epistaxis, menorrhagia, GI bleeding, CNS trauma, hemarthrosis, or traumatic hemorrhage)	Initial dose 50 to 75 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment.
Type 2 (all variants) and Type 3	Minor (clinical indications above)	40 to 50 IU/kg (1 or 2 doses)
	Major (clinical indications above)	Initial dose of 60 to 80 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment.

Variances of up to 10% in dosing are permissible during treatment of bleeding episodes, but rounding to the nearest vial size should be avoided.

Subjects with non-neutralizing binding anti-VWF antibodies should initially be treated with a dose known to be efficacious based on the subject's medical treatment history which may differ from the recommendations provided in Table 2. Subjects should be monitored for lack of efficacy as well as for FVIII (mandatory), VWF:RCo (mandatory), and VWF:Ag (optional where testing is not available) levels after 3 - 6 hours. Re-dosing with rVWF in combination with ADVATE using the same (initial) dose and adaptation of the dosing frequency should be considered until cessation of the bleed, if the FVIII and/or VWF:RCo levels drop below 30%-50% depending on bleeding severity.

The number of subsequent infusions and the dosage levels prescribed will be determined by the investigator on the basis of the clinical severity, response to current therapy, available laboratory data, and the subject's historical treatment for similar bleeding episodes.

8.7.5 Investigational Product Accountability

The investigator will ensure that the IP(s) is stored as specified in the protocol and that the storage area is secured, with access limited to authorized study personnel. The investigator will maintain records that the IP(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. IP(s) must be dispensed only at the study site or other suitable location (e.g. infusion center; home, as applicable per study design), as specified in the protocol (see Section 10). Records will be maintained that includes the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

8.8 Source Data

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

For additional information on study documentation and CRFs refer to Section 17.2. The use of subject diaries is described in Section 10.5.

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject has a documented diagnosis of severe VWD which
   a) is confirmed by genetic testing and multimer analysis, documented in patient history or at screening
   b) requires prophylactic replacement treatment with VWF containing concentrate to control bleeding. This includes:
      - subjects already on prophylactic treatment
      - subjects currently on-demand treatment for whom prophylactic treatment is recommended according to standard of care at the center
   c) a minimum of documented 3 spontaneous bleeds requiring VWF treatment within 12 months prior to prophylactic treatment.
2. Availability of records to reliably evaluate type, frequency and treatment of bleeding episodes prior to onset of prophylactic treatment for at least 12 months
3. Subject is ≥ 18 years old at the time of screening.
4. If female of childbearing potential, subject presents with a negative pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.
5. Subject is willing and able to comply with the requirements of the protocol.

9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

1. The subject has been diagnosed with pseudo VWD or another hereditary or acquired coagulation disorder other than VWD (eg qualitative and quantitative platelet disorders or elevated PT/ international normalized ratio [INR] >1.4).
2. The subject has a history or presence of a VWF inhibitor at screening.
3. The subject has a history or presence of a FVIII inhibitor with a titer ≥ 0.4 BU (by Nijmegen modified Bethesda assay) or ≥ 0.6 BU (by Bethesda assay).
4. The subject has a known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins.
5. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
6. The subject has a medical history of a thromboembolic event.

7. The subject is HIV positive with an absolute Helper T cell (CD4) count $<200/mm^3$.
8. The subject has been diagnosed with significant liver disease as evidenced by any of the following: serum alanine aminotransferase (ALT) 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).
9. The subject has been diagnosed with renal disease, with a serum creatinine level ≥ 2.5 mg/dL.
10. The subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to signing the informed consent.
11. The subject is pregnant or lactating at the time of enrollment.
12. The subject has participated in another clinical study involving another IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
13. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
14. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
15. The subject suffers from a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
16. The subject is in prison or compulsory detention by regulatory and/or juridical order
17. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.

9.3 Delay Criteria

1. If the subject has an acute bleeding episodes or presents with an acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) the screening visit will be postponed until the subject has recovered.

9.4 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (i.e., reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the termination visit (including cases of withdraw or discontinuation) are described in Section 10.6 and Section 20.2.

Discontinuation (i.e., complete withdrawal from study participation) may be due to dropout (i.e., active discontinuation by subject) or loss to follow-up (ie, discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also will be withdrawn from treatment or discontinued from further study participation for the following reasons:

- The subject is scheduled for an extended treatment period >3 months with non-topical immunomodulating drugs other than anti-retroviral chemotherapy (e.g., α-interferon, corticosteroid agents [equivalent to hydrocortisone greater than 10 mg /day]) during the course of the study.
- Subjects with chronic hepatitis B or C develop ALT/aspartate aminotransferase (AST) levels exceeding 5 times the upper limit of normal for >1 month.
- Subjects who experience severe allergic reactions, e.g., anaphylaxis upon exposure to rVWF.
- Subjects who develop a neutralizing inhibitor to rVWF and/or ADVATE (biological assays).
- Subjects who demonstrate clinical signs of thrombotic events.
- The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through completion of the pregnancy and up to 1 year post delivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome.
- The subject begins lactating. IP exposure will be discontinued. The investigator will record a narrative description of the course of the baby's development.
- The subject is not compliant with the prophylactic treatment regimen and does not adhere to the frequency of IP administration. Once >30% of infusions are missed within a visit interval (3 months), the subject will be discontinued from further participation in the study.

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient who provides informed consent (i.e., signs and dates the informed consent form and assent form, if applicable) is considered enrolled in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (e.g., 090701) to be provided by the sponsor, 2- or 3-digit number study site number (e.g., 02) to be provided by the sponsor, and 3- or 4-digit subject number (e.g., 0003) reflecting the order of enrollment (i.e., signing the informed consent form). For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 090701-020003. All study documents (e.g., CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The study site is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

The overall study design is illustrated in the Figure 1. Details on the procedures to be performed at each study visit, including screening, are provided in Supplement 20.2 Schedule of Study Procedures and Assessments and Supplement 20.3 Clinical Laboratory Assessments.

10.3.1 Screening Visit

Written informed consent must be obtained from each subject before any study related procedures are performed. To initiate screening procedures, at least 72 hours must have elapsed since the last VWF administration and the subject must not be actively bleeding at the time of screening. The screening visit will be delayed if the subjects presents with an acute bleeding episodes or acute illness (e.g. influenza, flu-like symptoms, inflammatory diseases) until the event has resolved. All screening procedures and confirmation of eligibility shall take place within 60 days prior to the first infusion of IP for PK assessments. If the IP is not infused within 60 days,

all screening assessments except blood group, human leucocyte antigen (HLA), genetics, multimeric pattern and [redacted], must be repeated to reconfirm eligibility. Refer to Supplement 20.2 and Supplement 20.3. Upon completion of screening procedures, subject eligibility will be confirmed by the sponsor on a subject eligibility form before additional study procedures are undertaken. The subject will maintain a diary that will include infusion logs, AEs, and concomitant medications (see Section 10.5). The allocation of IP will be initiated after the subject has qualified for home treatment (see Section 8.7.4.3.1).

In the event of a subject experiencing a bleeding episode that requires treatment between the screening visit and the baseline visit (PK assessment), the subject will be treated with rVWF. If rVWF is not available for any reason, e.g.: subject not yet trained on IP administration, study site visit for IP administration not feasible, etc., the subject may use his/her standard of care, such as commercial pdVWF/FVIII products. Subject currently on standard prophylaxis regimen with a commercial pdVWF/FVIII product may continue his/her regimen until initiation of rVWF prophylaxis (baseline – PK assessment visit) at the discretion of the investigator. In such cases, a minimum washout period of at least 5 days is required prior to infusion of rVWF for PK assessment (see Section 10.3.2 and Section 10.3.3).

10.3.2 Baseline Visit - PK-Assessment Visit

After screening and confirmation of eligibility each subject will undergo a PK assessment. Subjects transitioning from the surgery study **071101** will not need to undergo a PK baseline assessment again, provided valid PK data from **071101** is available. These subjects may proceed directly with the prophylaxis initiation visit (refer to Section 10.3.3) All subjects will receive a dose of 50± 5 IU/kg rVWF:RCo to determine VWF and FVIII levels. Blood samples will be drawn within 30 minutes pre-infusion, and at 7 time points post-infusion (30±5 minutes, 60± 5 minutes, 6±1 hours, 12 ± 1 hours, 24± 2 hours, 48± 2 hours, 72± 2 hours). IP infusion vials from the same lot number should be used for all PK-assessments per subject. Refer to Section 20.2 and Section 20.3. Samples for measurement of FVIII and VWF activity taken through to 6 hours post-infusion will be obtained from an extremity different from that used for the infusion of IP. Where needed, the phlebotomy site will be kept patent via an infusion of normal saline. In this event, at least 5 mL of blood will be collected and discarded before collection of the next test sample into a fresh syringe.

If the subject has a central venous catheter, the central line should be used to administer the infusion and a peripheral venipuncture should be used to collect the blood samples. In the event that a blood sample must be drawn through the central line used for administration of IP, the line must first be flushed with at least 10 mL normal saline or other suitable catheter flush solution that does not contain anticoagulant. At least 5 mL of whole blood must be collected and discarded prior to obtaining the sample.

If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.7.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment.

10.3.3 Prophylaxis Initiation Visit

After the blood sample for the 72 h PK assessment is drawn the subject will receive the first rVWF prophylactic dose of 50±10 IU/kg rVWF: RCo. Details on dose are provided in Section 8.7.4.3.

If a subject did not undergo PK assessment (for example the subject has transitioned from the surgery study **071101** and has undergone PK in this study, refer to Section 10.3.3.1), procedures and assessments at this visit include: adverse events, bleeding episodes, medications taken, non-drug therapies and laboratory assessment. Independent of previous PK assessment visits, within 2 hours prior the IP infusion, a physical examination will be performed. Vital signs will be assessed within 30 minutes prior to IP rVWF infusion and 30 minutes ±15 minutes after IP infusion. For subjects with a previous PK assessment in the course of the surgery study, incremental recovery (IR) will be determined based on VWF: RCo activity assessed prior and after IP infusion. Further details are provided in Supplement 20.2 and Supplement 20.3.

10.3.3.1 Surgical Prophylaxis

Subjects who require surgery during the study can be temporarily transferred to study **071101** (Surgery study) for their peri-operative and post-operative hemostatic management. The subject will be transferred to the Surgery study once Informed Consent for the Surgery study has been signed. Refer to the Surgery study protocol for further details.

The two studies are managed separately and the amount of transferrable data is limited. However, to minimize subject efforts and the number of blood draws, coinciding of study visits is feasible. For example, the screening visit for the Surgery study may be aligned with one of the foreseen follow-up visits of this prophylaxis study.

In this case, assessment results and laboratory values obtained at this consolidated study visit will be made available for both studies. Subjects transferred to the Surgery study **071101** will stop prophylactic treatment in this current prophylaxis study and adhere to the treatment regimen in the Surgery study (preoperative priming and loading dose, intra- and postoperative dosing) as described in the Surgery protocol. Subjects are expected to participate in the Surgery study for 8 to 15 weeks.. The termination visit of the Surgery Study may be used to confirm eligibility for transferring the subject back to this prophylactic study **071301**. Thereafter, the subject shall continue with the infusion of IP according to the prophylactic treatment regimen. The regular follow-up visits for the **071301** study will be re-scheduled accordingly, calculating from the time point the subject has restarted his/her previous prophylactic treatment regimen. The safety and efficacy data recorded while the subject was enrolled in the Surgery study will only be considered for the evaluation and assessment of the final results and conclusion of the Surgery study, but not for the assessment of efficacy and safety of this prophylaxis study.

10.3.4 Treatment of Bleeding Episodes

Treatment of bleeding episodes is described in detail in Section 8.7.4.4.

10.3.5 Follow-Up Visits (1 Month ± 1 Week, 2 Months ± 1 Week, 3 Months ± 2 Weeks, 6 Months ± 2 Weeks, 9 Months ± 2 Weeks)

Visits will be performed after the prophylaxis initiation visit at 1 month ± 1 week, 2 months ± 1 week and 3 months± 2 weeks and thereafter every three months± 2 weeks. Additional visits may occur if clinically indicated (see Section 10.3.6).

Within 2 hours prior to the rVWF IP infusion , a physical examination will be performed. Vital signs will be assessed within 30 minutes prior to IP infusion and 30 minutes ±15 minutes after IP infusion. Incremental recovery (IR) will be determined at each follow-up visit based on VWF:RCo activity assessed prior to and after IP infusion.

The blood sample for incremental recovery (IR) analysis will be drawn within 30 minutes prior to IP infusion and 30 minutes ±5 minutes after IP infusion. rVWF will be infused at the regular prophylactic dose, i. e 50 ± 10 IU/kg rVWF:RCo. For each subject's recovery analysis IP infusion, vials from the same lot number should be used.

Testing for VWF:RCo VWF:CB, rVWF:Ag, INNOVANCE VWF:Ac (exploratory) and FVIII:C level will be performed using the blood sample obtained before and after IP infusion.

The blood sample prior to IP infusion will also be used for the assessment ofinhibitory and binding antibodies, clinical chemistry and hematology. A washout period of at least 72 hours after the last infusion applies before the blood draw for the immunogenicity assays. Bleeding episodes, the hemostatic efficacy and AEs will be evaluated based on the review of the patient diary. Refer to Section 20.2 and Section 20.3. The evaluation of IP consumption and treatment compliance will be performed based on subject's diary entries. If a subject is not compliant with the prophylactic treatment regimen and does not adhere to the required frequency of administration of IP infusions [>30% of infusions were missed within a visit interval (3 months)] the subject will be withdrawn from the study.

At the 6 months ± 2 week visit an electrocardiogram (ECG) will be performed and [redacted] data will be collected. For the hemostatic efficacy assessment the following information will be recorded by the subject or by authorized study site personnel in the patient diary: bleeding location, type, severity, onset and resolution date and time, infusion date and time, clinical efficacy according to the rating scale. If at any time during the study a subject's bleeding episode does not adequately respond to rVWF therapy, he/she will be evaluated for the presence of inhibitory and total binding antibodies. Refer to Section 12.9.3.2.

Further guidance on completing the subject's diary will be provided to the subjects during training for home treatment (see Section 8.7.4.3.1).

10.3.6 Unscheduled Visits

For any unscheduled visit (except for collection of IP) a clinical assessment will be performed as per the scheduled follow-up visits with the exception of [redacted], ECG and IR determination (refer to Supplement 20.2 and Supplement 20.3.).

Subjects who have more than one bleeding episode in 3 months, or an increased frequency of bleeding, should go to the study site for an unscheduled visit.

Follow-Up visits after the subject has experienced a bleed may be requested by the investigator. Additional assessments may be required which are at the discretion of the investigator.

10.3.7 Study Termination Visit (12 months ± 2 weeks)

A washout period of at least 72 hours is required between the last infusion and the study termination visit. The following assessments will be performed after the last infusion of rVWF and at the time of early termination, if possible: vital signs, physical examination, clinical chemistry, hematology, rVWF:RCo, rVWF:CB, rVWF:Ag assays and FVIII:C and immunogenicity assays (refer to Supplement 20.2 and Supplement 20.3). A review of all AEs, bleeding episodes and the subject's diary and the [redacted] will be conducted at the termination visit.

10.4 Medications and Non-Drug Therapies

The following medications and non-drug therapies are **not** permitted within 30 days before study entry and during the course of the study:

Medications:

- 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) and an extended treatment period >3 months.
- Another investigational and/or interventional study drug (except rVWF and FVIII administered under the surgery protocol).

A subject who has taken any of these medications or received any of these non-drug therapies during the study will be withdrawn from the study.

The following medications are permitted during the course of the study:

- Antifibrinolytics (e.g., tranexamic acid, ε-amino caproic acid) or topical hemostats as needed, according to each institution's standard of care
- Emergent use of a VWF concentrate other than rVWF may be permissible under certain circumstances (see Section 8.7.4.4.1)

Details of all adjunctive hemostatic medication used, including dose and reason for use, will be recorded in the eCRFs.

10.5 Subject Diary

1. An electronic subject diary will be provided to each subject at the baseline visit to record the following information:
   - IP infusions to include date, start and stop times of the infusion, number of vials utilized, infusion volume, potency and lot numbers for prophylactic treatment or treatment of bleeding episodes, including IP infusion for PK analysis and other infusions at the study site
2. Details of bleeding episodes (site and type of bleeding) and response to treatment as described in Section 8.7.4.4
3. Subjective hemostatic efficacy assessments
4. Body weight
5. All AEs
6. Concomitant medications taken (including immunizations and infusions other than IP) and non-drug therapy.
7. Drug accountability (number of unused vials of investigational product remaining in the subject's refrigerator including refrigerator temperature as recorded, prior to each study visit).

Subjects and/or their legally authorized representatives will be trained on use of the diary. The diary will be provided in electronic format and remain with the subject for the duration of the study. The investigator will review the diary for completeness and request missing information periodically and in a timely manner. Untoward events recorded in the diary will be reported as AEs according to the investigator's discretion and clinical judgment.

Subject entries in the diary will serve as source records. During study participation the investigator has access to the database holding the subject diary data. After study closure, the investigator will receive the diary records for their subjects, including audit trail records, in PDF format. The data will be transmitted to the CRF by a validated transfer.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have completed all study procedures according with the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, AE (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, e.g., technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the study completion/termination visit. If the completion/termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the completion/termination visit. If a subject terminates participation in the study and does not return for completion/termination visit, his/her last recorded assessments shall remain with the last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.2 Schedule of Study Procedures and Assessments and Supplement 20.3 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

10.7 Procedures for Monitoring Subject Compliance

Subject compliance with the procedures of this study (treatment regimens and study visits) will be monitored by the investigator or/a licensed healthcare professional at the study site.

During the regular scheduled follow-up visits a direct review of the subject's source data (e-diaries) will be performed at the sites and evaluated against the protocol requirements. In addition drug accountability will be evaluated at each follow-up study visit and the study termination visit by comparing the infusions recorded in the subject diary with empty vials returned by each subject to the study site, and the study site's dispensing record. Protocol deviations will be noted in the final report.

11. ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

11.1 Assessment of Spontaneous Bleeding Episodes/Annualized Bleed Rate

The annualized bleed rate (ABR) will be assessed based upon each individual spontaneous bleed, requiring coagulation factor replacement therapy, i.e. rVWF treatment. The following details on bleeding episodes will be recorded by the subject (for home treatment), the subject's healthcare provider (for treatments away from the primary investigative site), or by authorized, qualified personnel at the participating site (for hospital-based treatment) in the subject's diary:

- Location of bleed; i.e., joint, menorrhagia, epistaxis, gastrointestinal, soft tissue, muscle, body cavity, intracranial, etc.
- Type of bleed; i.e., spontaneous, traumatic, unknown
- Severity of bleed; i.e., minor, moderate, and major
- Date and time of onset of bleed
- Date and time of each infusion of rVWF or rVWF-ADVATE used to treat a bleeding episode
- Date and time of resolution of the bleeding episode
- Type and number of analgesics as well as additional hemostatic treatments required
- Other concomitant medications
- Non-drug therapies
- AEs (refer to Section 12.1)

Study site personnel are qualified after they have undergone training during the qualification of the site.

All types of bleeds, including traumatic bleeds, will be recorded, however only spontaneous bleeds requiring VWF treatment will be considered for the assessment of ABRs used for primary outcome assessment .

Bleeds occurring at the same anatomical location (e.g., right knee) with the same etiology (i.e., spontaneous versus injury) within 24 hours after onset of the first bleed will be considered a single bleed. Bleeding occurring at multiple locations related to the same injury (e.g., knee and ankle bleeds following a fall) will be counted as a single bleeding episode.

All efforts should be made to use rVWF for treatment of bleeding episodes. If needed the use of a VWF concentrate other than IP for the treatment of bleeding episodes will not disqualify the subject from further participation in the study and will not be considered a protocol deviation.

11.2 Evaluation of ABR before rVWF Prophylaxis and ABR under rVWF prophylactic treatment

At screening, the subject's medical history will be recorded, including the number of all spontaneous bleeding episodes within the past 12 months on-demand treatment. The ABR during the 12 months before prophylactic treatment will be the baseline for evaluation of ABR under rVWF prophylactic treatment. If applicable, the ABR determined during previous prophylactic treatment using a commercial pdVWF/FVIII product will also be recorded. The maximum interval of bleed-free periods as well as trauma induced bleeding episodes will also be recorded.

11.3 Number of Infusions and Total Weight Adjusted Consumption of rVWF and ADVATE

The number of rVWF and ADVATE (in case of bleeding episode treatment) infusions will be logged in the subject diary. Based on these entries the weight adjusted consumption will be calculated per month and per year.

11.4 Assessment of Efficacy for Treatment of Bleeding Episode

Investigators will be asked to assess and record hemostatic efficacy after resolution of each bleeding episode using the 4-scale rating system outlined in Table 3.

Table 3
Hemostatic Efficacy Rating Scale [12]

Rating Scale	Definition
Excellent	Hemostasis achieved/complete cessation of bleeding
Good	Slight oozing/partial but adequate control of bleeding did not require additional product for unplanned treatment
Moderate	Moderate bleeding/moderate control of bleeding; required additional product for unplanned treatment
None	Severe uncontrolled bleeding

11.5 Pharmacokinetic Assessment

Details on pharmacokinetic assessments are provided in Section 12.9.1.

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

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, whether or not considered causally related to the IP.

12.1.1.1 Serious Adverse Event

A **serious** adverse event (SAE) is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are:
  - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
  - Reviewed and confirmed seroconversion for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)
  - Development of inhibitory VWF antibodies
  - Development of inhibitory antibodies to FVIII (titer ≥ 0.4 BU (by Nijmegen-modified Bethesda assay) or ≥0.6 BU (by Bethesda assay))

- Thromboembolic events (e.g., myocardial infarction, stroke, transient ischemic attack (TIA), deep vein thrombosis (DVT) or pulmonary embolism)
- Anaphylactic type hypersensitivity reactions (for definition, refer to Section 12.6.2)

Uncomplicated pregnancies, following maternal or paternal exposure to IP are not considered an (S)AE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE.

12.1.1.2 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet the criteria of an SAE.

12.1.1.3 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (e.g., IB, package insert). "Unexpected" also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.1.1.4 Preexisting Disease

Preexisting diseases that are present before entry in to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described on the AE CRF.

12.1.2 Assessment of Adverse Events

For the purposes of this study, the following will not be considered as AEs and will not be included in the analysis of AEs.

- Bleeding episodes are part of the underlying disease and therefore are not AEs; they will be evaluated in the context of efficacy. If a bleeding episode was caused by an injury, the injury would not be reported as an AE, unless it resulted in a medical finding other than a bleeding episode (e.g., abrasion of skin). Therefore, any VWD-related bleeding event (e.g., epistaxis, gastrointestinal bleeding, musculo-skeletal bleeding, menorrhagia) will not be reported as AEs. However, the investigator may decide that the event is an AE if the event also would have occurred in a healthy individual under the same circumstances.

- Seroconversion after documented HAV/HBV vaccination prior to or during the study period.

Each AE from the first IP exposure to the study completion date will be described on the AE CRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2

For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution.

If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the protocol-specified dosage (including underdosing /overdosing [< 20 IU/kg rVWF:RCo or > 100 rVWF:RCo], abuse, and withdrawal, treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after administration of IP will be reported on a Pregnancy Form and followed-up at 1 year post-delivery, if feasible.

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the SAE Form within 24 hours after awareness: no additional reporting on CRFs is necessary.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, e.g., assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

Not related (both circumstances must be met)

- Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
- Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).

Unlikely related (either 1 or both circumstances are met)

- Has little or no temporal relationship to the IP
- A more likely alternative etiology exists

Possibly related (both circumstances must be met)

- Follows a reasonable temporal relationship to the administration of IP
- An alternative etiology is equally or less likely compared to the potential relationship to the IP

Probably related (both circumstances must be met)

- Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
  - Reappearance of a similar reaction upon re-administration (positive re-challenge)
  - Positive results in a drug sensitivity test (skin test, etc.)
  - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
- Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within 5 days after IP infusion, the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical trial or trials
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor.

In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committee is notified of the urgent measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (i.e., from the time of signed informed consent up to but not including the first IP exposure) will be described on the SAE Report. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE.** NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g. reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (e.g., potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) 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. The subject's medical history will also include documented history of on-demand and prophylactic treatment for the past 12 months and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 months.

All medications taken and non-drug therapies received in the 2 weeks prior to study entry and all concomitant medications and non-drug therapies during study will be recorded on the CRFs.

Data on medical history, drug and non-drug therapy history of those subjects who transition from surgery rVWF study will be used from the eCRF of the main studies, will be updated, if applicable, and transcribed into the respective eCRF of the prophy study.

12.6 Physical Examinations

At screening and subsequent study visits (as described in Section 10.3), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 12.1.1.4), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.6.1 Thromboembolic events

Thromboembolic events are considered a potential risk of rVWF treatment, hence, indices of thromboembolic events such as clinical evidence of thrombosis will be monitored during the study. In the case of clinical signs of any thrombotic event other than superficial thrombosis, additional diagnostic procedures are required according to each institution's standard of care which may consist of, but are not limited to the following:

- For deep vein thrombosis (DVT): Magnetic Resonance Imaging (MRI), compression ultrasound or impedance plethysmography.
- For pulmonary embolism: ECG, chest radiography, perfusion/scintiscan or MRI.
- For myocardial infarction: ECG, cardiac enzymes, echocardiography
- For stroke: diffusion-weighted magnetic resonance imaging or computed tomography, ABCD scoring, carotid imaging

Results of diagnostic procedures may be forwarded to the sponsor to be reviewed by an independent external expert panel, such as the DMC, if applicable.

12.6.2 Anaphylactic reactions

Anaphylaxis is highly likely when any of the following 3 criteria are fulfilled:

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
    b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a. Involvement of the skin or mucosal tissue (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c. Reduced BP or associated symptoms (hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3) Reduced BP after exposure to a known allergen for that patient (minutes to several hours):
    a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
    b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP

If a subject develops a severe allergic reaction (e.g., anaphylaxis) in the course of the clinical study this needs to be reported as SAE (Section 12.1.1.1). Additional blood draws for Anti-VWF IgE antibody testing will be drawn (Section 12.9.13).

12.7 Vital Signs

Vital signs will be assessed pre and post-infusion at each visit, if not stated otherwise:

- Height (cm) and weight (kg)
- Blood pressure: Systolic/diastolic blood pressure (mmHg) baseline measurements will be measured after a 10-minute rest in the supine/semi-recumbent position.
- Pulse rate: Pulse rate (beats/min) will be measured at the distal radial arteries under the same conditions as above.
- Respiratory rate: Respiratory rate (breaths/min) will be measured over a period of 1 minute under the same conditions as above.
- Temperature: Body temperature (^{o}C or ^{o}F) may be determined by oral, rectal, axillary, or tympanic measurement at the discretion of the investigator. However, the same method should be used for all measurements in 1 subject.

Vital signs (pulse rate, respiratory rate, and blood pressure) should be recorded within 30 min before and after IP administration. The assessment of vital signs per planned study visit is outlined in Supplement 20.2.

Vital sign values are to be recorded on the physical examination eCRF. For each vital sign value, the investigator will determine whether the value is considered an AE (see definition in Section 12.1). If assessed as an AE, the medical diagnosis (preferably), symptom, or sign, will be recorded on the AE eCRF. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE, should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.8 Electrocardiogram

A standard 12-lead ECG at rest will be performed at screening, at the 6 month follow-up visit and at the study termination visit and evaluated for medical significance by the investigator.

12.9 Clinical Laboratory Parameters

Refer to the Laboratory Manual for information on collection and processing of samples.

In general all laboratory tests will be performed at central laboratories, except the pregnancy and blood group test which will be performed at the local laboratory. In addition, relevant critical safety laboratory tests for complete blood count (CBC), serum chemistry and/or coagulation parameters such as VWF and FVIII activity may also be performed in the local laboratory to ensure that results will be available immediately to the investigator. In principle, results from the central laboratory will be used for data analysis purposes. The assays performed in the central laboratories are specified in the Laboratory Manual. The investigator will supply the sponsor with a list of the normal ranges and units of measurement for the laboratory variables to be determined at the site. Laboratory values such as antibodies to other proteins are not required immediately and will be assessed later during the course of the study. Any remaining samples not required for the purpose of this study may be used for non-commercial dedicated VWF and/or VWD research to improve the diagnosis and treatment.

Abnormal laboratory values deemed clinically significant by the investigator are to be recorded as AEs (see Section 12.1.2).

12.9.1 rVWF and endogenous FVIII Pharmacokinetics

PK assessments using a dose of 50 IU±5 IU/kg rVWF:RCo will be performed at the baseline visit. If the subject is on prophylactic treatment using a commercial pdVWF/FVIII product or is on on-demand treatment and has received VWF replacement therapy a washout period of at least 5 days is required before the infusion of rVWF for PK assessment can be administered. If a subject is on prophylactic treatment using a pdVWF product as standard care, the subject has to terminate the prophylactic treatment using rVWF immediately at least 5 days before the PK assessment is started (see further details in Section 10.3.1).

Blood samples will be drawn within 30 minutes pre-infusion, and at 7 time points post-infusion (30±5 minutes, 60± 5 minutes, 6±1 hours, 12 ± 1 hours, 24± 2 hours, 48± 2 hours and72± 2 hours) VWF activity will be determined using the VWF:RCo, VWF:CB and the VWF: Ag assay. The Innovance assay will be used as an exploratory assay to provide supportive data and to compare the results of this new assay with results from the established VWF:RCo assay.

Endogenous FVIII activity will be measured using the 1-stage clotting assay.

The following parameters will be used as part of the PK assessment:

- Incremental recovery of VWF:RCo, VWF:Ag, VWF:CB and INNOVANCE VWF Ac (exploratory assay)
- AUC/dose, area under moment curve (AUMC/dose, clearance (CL), Volume of distribution at steady state (V_{ss}), mean residence time (MRT), of VWF:RCo ,VWF:Ag, VWF:CB and INNOVANCE VWF Ac (exploratory assay)
- Half-life of VWF:RCo, VWF:Ag, VWF:CB and INNOVANCE VWF Ac (exploratory assay)
- Time course of the FVIII:C levels
- VWF collagen binding (VWF:CB) levels

12.9.2 Hematology and Clinical Chemistry

The hematology panel will consist of CBC [hemoglobin, hematocrit, erythrocytes (ie, red blood cell count [RBC]), and leukocytes (i.e., white blood cell count [WBC])] with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.

The clinical chemistry panel will consist of sodium (Na), potassium (K), chloride (Cl), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), bilirubin (BILI), alkaline phosphatase (AP), blood urea nitrogen (BUN), creatinine (CR), and glucose (Glu).

Blood will be obtained for assessment of hematology and clinical chemistry parameters at screening, during PK-assessment prior to rVWF IP infusion, after 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours post rVWF IP infusion, at all follow-up visits as per schedule (refer to Supplement 20.3 Clinical Laboratory Assessments), i.e., 4 weeks ± 1week, 8 weeks ± 1 week and every 3 months ± 2 weeks, and at study completion/termination. Hematology and clinical chemistry assessments will be performed on Ethylenediaminetetraacetic acid (EDTA)-anticoagulated whole blood and serum, respectively, at the central laboratory.

12.9.3 Immunology

12.9.3.1 Antibodies to VWF and FVIII

All subjects will be tested for binding and inhibitory antibodies to VWF and FVIII at screening, at baseline PK assessment, at each of the scheduled follow-up visits and at the study completion visit. Testing will be done prior to IP infusion and with at least a 72 hour wash out period since the last IP infusion. If there is any suspicion of inhibitor development (e.g. excessive bleeding) binding and inhibitory antibodies to VWF and FVIII may be tested at the discretion of the investigator.

12.9.3.2 Inhibitory and Total Binding Anti-VWF Antibodies

The assays to establish the presence of neutralizing and total binding anti-VWF antibodies have been established in the absence of international standards and with only limited numbers of positive controls. Therefore, caution is advised in interpreting positive results. In particular, any clinical association, changes in the natural history of the disease, effect of therapy, etc. needs to be taken into account for final judgment. The sponsor's Medical Director should be consulted for additional advice. As part of the AE follow-up, any sample testing positive needs to be confirmed after 2-4 weeks for central laboratory testing. Only confirmed neutralizing anti -VWF antibodies are considered inhibitors (see Section 12.9.3.4). These subjects need to be closely monitored and therapy adjusted accordingly.

12.9.3.3 Binding antibodies to VWF

The presence of total binding anti-VWF antibodies will be determined by an enzyme-linked immunosorbent assay (ELISA) employing polyclonal anti-human Immunoglobulin (Ig) antibodies (IgG, IgM and IgA). For this assay (ELISA), recombinant human VWF will be coated onto a microtiter plate, then incubated with dilutions of the positive control, the negative control or test sample. Antibodies against human VWF that are present in the samples bind to the coated antigen and will be detected with a horseradish peroxidase (HRP)-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a human monoclonal antibody specific for human VWF spiked into the negative control. The negative control for this assay is pooled normal human plasma.

Plasma samples are analyzed for binding antibodies against the specific antigen in two steps. First, the sample is screened for antibodies and the titer of binding antibodies is determined. Second, the specificity of positive antibody results is confirmed.[13] In brief, all samples are serially diluted (initial dilution 1:20 and further diluted 1:2). The titer endpoint, defined as the highest dilution that still gives a positive signal above cut off level, is determined in two independent duplicates. The cut off level is established based on background signal level of healthy plasma donors (n=160) and set to include 5% false positives to be as sensitive as possible (95% percentile). The ELISA assay is validated allowing an assay variability of ± 1 titer step. Therefore, differences ≤ 2 titers steps may be due to variability of the ELISA assay. Specificity has to be confirmed in a competition assay when a sample has a titer of 1:80 or higher in the screening assay. Based on the validation criteria samples tested in the screening assay at 1:20 or 1:40 cannot be confirmed in the competition assay. A positive screening value is confirmed if the difference between the titers determined for the subject sample (re-screen) and for the

subject sample with pre-incubation (confirmation sample) is > 2 titer steps. Antibody titers of subject samples will only be reported as positive, if the results of the screening and confirmatory analysis fulfill these acceptance criteria. The titer to be reported is always the one determined in the original screening procedure (independent of the result of the re-screening in the confirmation procedure).

A more detailed test procedure will be supplied upon request or pro-actively if a sample tests positive. A treatment related increase of the binding anti-VWF antibodies is expected, if the titer increases by more than 2 titration steps. These subjects need to be closely monitored and therapy adjusted accordingly.

12.9.3.4 Neutralizing antibodies to VWF

Three functional VWF assays, collagen binding (VWF:CB) assay, Ristocetin cofactor (VWF:RCo) and FVIII binding (VWF:FVIIIB), will be used to test for the presence of inhibitory anti-VWF antibodies. Neutralizing antibodies to VWF:RCo, VWF:CB and VWF:FVIIIB activities will be measured by assays based on the Bethesda assay established for quantitative analysis of FVIII inhibitors (Nijmegen modification of the Bethesda assay).[14] The amount of inhibitor is expressed as Bethesda units (BU) per mL. One BU is thereby defined as the amount of inhibitor that decreases the measured activity in the assays to 50% of that of the negative control samples. The assays were validated using human plasma samples from two type 3 VWD patients with low (1-2 BU/mL) and high (~10 BU/mL) titer inhibitors and plasma samples from non-human primates immunized with human rVWF (>100 BU/mL)

If a subject has a measurable baseline level of VWF activity in the respective assay, it is taken into account in the calculation of the residual activity. However, if baseline levels are too high (>15% VWF:RCo), inhibitors may not be reliably detected.

To exclude false positive results, the detection limit for anti-VWF inhibitors was set to 1 BU/ml for all 3 assays. The rationale for this cut-off value is the relatively high confidence interval of the underlying assays, making determinations at the end of the evaluation range of the Bethesda reference curve uncertain.[15]

A more detailed test procedure may be requested to further characterize the anti-VWF inhibitors, if detected.

12.9.3.5 Binding Antibodies to FVIII

Binding antibodies against FVIII will be analyzed using a proprietary enzyme immunoassay. The testing strategy will be as described for binding anti- VWF antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.3.6 Neutralizing antibodies (inhibitors) to FVIII

Neutralizing antibodies (inhibitors) to FVIII will be assessed by the Nijmegen modification of the Bethesda assay in a central laboratory. To verify a FVIII inhibitor, additional testing (such as tests for Lupus anticoagulants) may be initiated. Positive FVIII inhibitor tests will be defined as ≥ 0.4 BU by the Nijmegen-modified Bethesda assay that is confirmed by a second test performed on an independent sample obtained 2-4 weeks following the first test. Only confirmed positive FVIII inhibitor test result will be reported as an SAE.

12.9.4 Antibodies to Other Proteins

Plasma will be assayed for the presence of antibodies against CHO protein (total Ig), murine IgG and human Furin (total Ig) using proprietary enzyme immunoassays. The testing strategy will be as described for binding anti- VWF antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.4.1 Anti-CHO Protein

Total Ig antibodies (IgG, IgA, IgM) against CHO protein will be analyzed. For this assay (ELISA), CHO protein derived from cultures of untransfected cells and propagated under the identical cell culture conditions used for ADVATE production will be coated onto a microtiter plate, then incubated with dilutions of the positive control, negative control or test sample. Antibodies against CHO protein that are present in the samples bind to the coated antigen and will be detected with a horseradish peroxidase (HRP)-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a polyclonal goat anti-CHO protein antibody spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.4.2 Anti-Murine IgG

A commercially available ELISA (Medac, Hamburg, Germany) will be used to detect and to quantify IgG antibodies originating from human plasma that are directed against mouse-IgG (HAMA: human anti- mouse antibodies). Microtiter plates coated with mouse IgG will be incubated with dilutions of the standard, the positive control, the negative control or the test sample. Antibodies against mouse IgG that are present in the samples bind to the coated antigen and form a bridge to a peroxidase coupled mouse IgG antibody that will be used for detection (bridging format of the ELISA assay). The positive control for this assay will be a polyclonal goat anti-murine IgG spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.4.3 Antibodies to human Furin

Total Ig antibodies (IgG, IgA, IgM) against human Furin will be analyzed. For this assay (ELISA), recombinant human Furin will be coated onto a microtiter plate, then incubated with dilutions of the positive control, the negative control or test sample. Antibodies against human Furin that are present in the samples bind to the coated antigen and will be detected with a horseradish peroxidase (HRP)-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a human monoclonal antibody specific for human Furin spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.5 Viral Serology

The following viral seromarkers will be assessed at screening:

- HIV: anti-HIV 1, HIV 2
- HAV: anti-HAV (IgG and immunoglobulin M [IgM])
- HBV: Hepatitis B surface antigen (HbsAg), anti-Hepatitis B (HB) core, anti-HBs
- HCV: anti-HCV ELISA
- Parvovirus B19: anti-B19V (IgG and IgM)

Virus serology will be established during the screening period. The relevant confirmatory Polymerase Chain Reaction (PCR) testing may be performed from appropriate left-over samples as needed.

12.9.6 Urinalysis (Dipstick)

The urinalysis will include assessments for erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite and pH and will be performed at the central laboratory.

12.9.7 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. The pregnancy test may need to be repeated during the course of study in countries where mandated by national law.

12.9.8 VWD Mutational Analysis, Multimer Analysis and Human Leukocyte Antigen Genotyping

A cell pellet (buffy coat and erythrocytes) will be retained for VWD gene mutational analysis and HLA genotype determination if the information is not already available in the subject's medical history. Results from multimer analysis (see Section 12.9.10.1) may contribute to VWD gene mutational analysis. The genetic testing will be done, when the subject consents to the genetic testing.

12.9.9 Blood Group Analysis

The blood group needs to be determined during the screening period. If the information is not already available in the subject's medical history, it has to be determined at the local lab.

12.9.10 Additional Laboratory Testing in case of Thrombotic Events

rVWF contains ultra large molecular weight (ULMW) multimers because of a lack of exposure to endogenous VWF protease (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) during the manufacturing process. In vitro and in vivo cleavage of these ultralarge molecular fractions by ADAMTS13 and generation of characteristic satellite bands has been extensively demonstrated during nonclinical and clinical development. Nevertheless, the potential elevated risk of thrombosis and/or other thromboembolic complications due to the administration of ultra large molecular VWF multimers in subjects with normal levels of VWF cannot be completely excluded. Therefore VWF multimer analysis will not only be performed routinely at screening but in case of thrombotic events both VWF multimer analysis as well as ADAMTS13 activity will be determined to assess any relatedness of these occurrences with IP treatment.

12.9.10.1 VWF multimers analysis

The VWF multimers pattern will be assessed using low-resolution sodium dodecyl sulfate (SDS)–agarose gel electrophoresis. High-resolution SDS–agarose gel electrophoresis, with agarose concentrations >1.5%, will be used to determine the satellite band structure of VWF. These analyses will employ Western blot with luminescence video imaging.

12.9.10.2 ADAMTS13 activity

VWF73 was identified as the 73 amino acid minimal region of the VWF A2 domain required for ADAMTS13 cleavage. The cleavage of this substrate will be detected by a commercially available ELISA-based Chromogenic assay (Technoclone Austria): Cleavage of immobilized VWF73 substrate is detected by a HRP-labeled antibody directed against the cleavage site of VWF73. The amount of bound antibody, which is the function of the ADAMTS13 cleavage is detected by a chromogenic substrate.

12.9.11 Soluble P-Selectin (sP-Selectin)

sP-selectin is a cell adhesion molecule (CAM) found in granules in endothelial cells (cells lining blood vessels) and activated platelets. Data for an association between the sP-selectin concentration, thrombotic thrombocytopenic purpura (TTP) and venous thromboembolism (VTE) are limited and the predictive value has not yet established. A commercial ELISA assay will be employed as an exploratory test. sP-selectin will be determined at the Screening visit and used as indicator for an increased thrombotic risk.

12.9.12 D-Dimer

D-dimer will be used as a marker for DVT and disseminated intravascular coagulation (DIC). While a negative result practically rules out thrombosis, a positive result can indicate thrombosis but does not rule out other potential etiologies, including a recent hemorrhage. Its main use, therefore, is to exclude thromboembolic disease where the probability is low. D-Dimer will be measured at the Screening visit and used as indicator for an increased thrombotic risk.

12.9.13 Additional Laboratory Testing in Case of Severe Allergic Reactions (e.g. Anaphylaxis)

If a subject develops a severe allergic reaction (e.g. anaphylaxis) in the course of the clinical study, additional blood draws for anti-VWF IgE antibody testing will be drawn. The presence of anti-VWF IgE will be determined by using the ImmunoCAP®, a VWF-specific IgE blood test (Thermo Scientific). The basis of the ImmunoCAP® technology is a cellulose polymer as solid phase in a plastic capsule providing a large surface for protein binding. rVWF as antigen is covalently coupled to the cellulose polymer. Detection of specific anti-VWF IgE bound to the antigen will be accomplished by a secondary enzyme-labeled anti-human IgE antibody. Testing for binding anti-human VWF IgE antibodies will be done with 0.5 mL plasma. Antibody containing samples will be identified and quantified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.14 Exploratory Assay

The INNOVANCE VWF Ac: an assay, which will eventually replace the VWF:RCo test in the future, will be done using the same time points/blood draws incl. PK assessment as outlined for the VWF:RCo assessments. The VWF Ac assay is a sensitive test for direct determination of VWF activity. It employs an advanced new technology, allowing the assay to mimic the reaction in which VWF binds to glycoprotein Ib (GPIb), the major VWF receptor protein on platelets. Latex particles are coated with an antibody against GPIb, to which recombinant GPIb is added.

12.9.15 Assessment of Laboratory Values

12.9.15.1 Assessment of Abnormal Laboratory Values

For VWF and FVIII laboratory assessments no evaluation of clinical significance is necessary.

Each other laboratory value (except results to determine genetics of the underlying VWD disease and blood group) has to be assessed by the investigator and the assessment will be recorded on the eCRF. The investigator will determine for each abnormal laboratory value whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 12.1) and record the sign, symptom, or medical diagnosis on the AE CRF, is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.4), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, i.e. because it is due to a preexisting disease, due to a lab error, due to variation or due to another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

Any seroconversion result for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V) shall be re-tested.

12.9.16 Biobanking

Backup samples should be taken and stored appropriately for additional analysis, if necessary. These samples may be used for re-testing, further evaluation of an AE, or follow-up of other test results.

The following samples are planned:

- Citrated plasma samples (minimum of 2,5 ml per sample) taken at:
  - Screening
  - Baseline Visit –PK assessment (within 30 minutes prior to IP infusion start and at 7 time points post infusion: 30 ± 5 minutes; 60 ± 5 minutes; 6 ± 1 hours; 12 ± 1 hours; 24 ± 2 hours; 48 ± 2 hours; 72 ± 2 hours);
  - Prophylaxis initiation visit
  - Follow-up visits (1 month ± 1 week, 2 months ± 1 week, 3 months ± 2 weeks, 6 months ± 2 weeks, 9 months ± 2 weeks after the Prophylaxis initiation visit)
  - Study completion/termination visit

Backup samples that remain after study testing is done may be stored and used for additional testing (e.g., further evaluation of an abnormal test, an AE or assay development) and further assay developments. Samples will be stored in a coded form for a maximum of 2 years after the final study report has been completed and then the samples will subsequently be destroyed.

12.10 [redacted]

12.10.1 [redacted]

12.10.2 [redacted]

[redacted]

13. STATISTICS

13.1 Sample Size and Power Calculations

The determination of the sample size for this study is not based on strict statistical considerations.

13.2 Datasets and Analysis Cohorts

13.2.1 Safety Analysis Set

The Safety Analysis Set will be comprised of all subjects who received any amount of IP, rVWF:ADVATE or rVWF alone.

13.2.2 Full Analysis Dataset

The Full Analysis Set (FAS) will be comprised of all subjects who received prophylaxis IP infusion for at least 6 months.

13.2.3 Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set will be comprised of subjects who are at least 70% compliant regarding required prophylactic infusions. Only subjects who met all study entry criteria and who had no major protocol violations that might impact efficacy assessments will be included in the PP analysis set.

13.2.4 PK Full Analysis Set

The Pharmacokinetic Full Analysis Set (PKFAS) will be comprised of all subjects who received the PK infusion and who provided acceptable data for PK analysis. Acceptable PK data will be defined in the Statistical Analysis Plan.

13.2.5 PK Per Protocol Analysis Set

The Pharmacokinetic 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 affecting the PK period of the study as defined in the detailed Statistical Analysis Plan.

13.3 Handling of Missing, Unused, and Spurious Data

13.3.1 General

Statistical techniques will not be used to identify and exclude any observations as outliers from the analyses. If data are considered spurious, e.g. for lack of biological plausibility, it will be documented to include the reason for exclusion and the analyses from which the data were excluded.

13.3.2 Other

1) Regarding missing data in PK records:

- Body weight: If a subject's weight is missing from the PK infusion record, the subject's last recorded weight will be used to calculate the weight-adjusted dose.
- Concentration:
- Baseline concentration levels reported as below the limit of quantification will be considered to be 0. Missing VWF baseline concentration levels (VWF: RCo, VWF: AG or VWF: CB) for Type 3 subjects will be set to 0.
- Time:
  - If start time of infusion is missing (but stop time is available) and actual collection time is available, then stop time of infusion will be taken for further calculation (i.e. time difference between actual end date/time of infusion and date/time blood sample drawn).
  - If actual collection date/time is missing and planned collection date/time is missing, then this PK time point will be taken out from the PK analysis (i.e. no data entry for this time point).
  - For all other scenarios, the planned collection date/time will be taken for further calculation.

2) Regarding missing data in AE records:

- Handling of unknown causality assessment:
  - If a subject experiences an AE with a missing causality assessment, the relationship of the AE will be counted as "related."
- Handling of unknown severity grades:
  - If a subject experiences more than one AE categorized under the same preferred term, 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.

13.4 Methods of Analysis

13.4.1 Primary Outcome Measure

The focus of the statistical analysis will be descriptive.

For the prospectively recorded overall annualized bleeding rate (ABR) of spontaneous bleedings during prophylactic treatment as well as for the historical ABR of spontaneous bleedings, means and corresponding 90% two-sided confidence intervals based on the negative binomial distribution will be estimated. The confidence intervals will be calculated within a generalized linear model framework (with a logarithmic link function which is the default for the negative binomial distribution), accounting for the logarithm of follow-up time (in years) as an offset.

The annualized rate of bleeding episodes will be calculated as (Number of bleeding episodes/observed treatment period in days) * 365.25.

The primary efficacy analysis will be based on the FAS. As a supportive analysis, the same analysis will also be carried out on the PP.

13.4.2 Secondary Outcome Measures

13.4.2.1 Efficacy

For the number of infusions and for the total weight adjusted consumption of rVWF and ADVATE per month and per year, summary statistics will be carried out.

For the number of subjects with reduction of ABR as well as for the number of subjects with 0 bleeds, proportions and corresponding 90% two-sided confidence intervals will be performed.

The secondary efficacy analysis will be performed on the FAS only.

13.4.2.2 Efficacy of the Treatment of Bleeding Episodes

For the number of infusions of rVWF and ADVATE per bleeding episode, for the weight adjusted consumption of rVWF and ADVATE per bleeding event as well as for the overall hemostatic efficacy rating at resolution of bleed, summary statistics will be carried out.

The analysis will be performed on the FAS.

13.4.2.3 Pharmacokinetic Analysis

All PK analyses will use the actual sampling times, not nominal times specified in the protocol, wherever possible. Actual sampling times will be defined as time from the start of infusion to the blood sample collection time. A deviation from the protocol-specified blood sample 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 results were biologically implausible will be eliminated from the analysis.

If any concentration data are considered spurious (e.g. lack of biological plausibility), the reason for exclusion from the analysis and the analysis from which the data point was excluded will be documented.

To ensure that values at baseline (pre-infusion) are not affecting the estimation of PK parameters, post-infusion concentration data will be adjusted for baseline as follows:

$$C_{\text{Corrected, t}} = (1 - \frac{C_{\text{Measured, pre-infusion}}}{C_{\text{Measured, Tmax}}}) \cdot C_{\text{Measured, t}}$$

After adjustment of the post-infusion concentration data, any pre-infusion data will be set to 0.

$C_{Corrected}$ will be set to missing, if:

- Samples have an unknown draw time or where the concentration could not be determined, or where results were deemed to be unreliable due to analytical issues.
- Any concentration data are considered spurious (e.g. lack of biological plausibility).

Handling of concentrations that are below the quantification limit:

- Baseline concentration values reported as below the limit of quantification will be considered to be 0 ($\rightarrow C_{Corrected}$ = Concentration value)
- Post-infusion concentration values reported as below the limit of quantification or missing repeated concentration values will be set to missing ($\rightarrow C_{Corrected}$ = missing)

The area under the plasma concentration/time curve from time 0 to infinity ($AUC_{0-\infty}$) and the area under the first moment curve from time 0 to infinity ($AUMC_{0-\infty}$) will be calculated as the sum of AUC or AUMC from time 0 to the time of last quantifiable concentration plus a tail area correction calculated as C_t/λ_z and $C_t/\lambda_z(t + 1/\lambda_z)$, respectively, where C_t is the last quantifiable concentration, t is the time of last quantifiable concentration and λ_z is the terminal or disposition rate constant.

The area under the plasma concentration/time curve from time 0 to 72 hours post-infusion ($AUC_{0\text{-}72h}$) will be computed using the linear trapezoidal rule. For the calculation of $AUC_{0\text{-}72h}$ the levels at 72 hours will be linearly interpolated/ extrapolated from the 2 nearest sampling time points.

Elimination phase half-life (HL) in hours will be calculated as:

$$T_{1/2} = log_e(2)/\lambda_z$$

where the elimination rate constant (λ_z) will be obtained by log_e-linear fitting using least squares deviations to at least the last 3 quantifiable concentrations above pre-infusion level.

The **Mean Residence Time** (MRT) in hours will be calculated as total area under the moment curve divided by the total area under the curve:

$$MRT = \frac{AUMC_{0-\infty}[h^2 * IU/dL]}{AUC_{0-\infty}[h * IU/dL]}$$

Systemic clearance in dL/kg/h will be calculated as the dose in IU/kg divided by the total AUC:

$$CL = \frac{Dose[IU/kg]}{AUC_{0-\infty}[h * IU/dL]}$$

Apparent **steady state volume of distribution** (Vss) in dL/kg will be calculated as:

$$Vss = \frac{Dose[IU/kg] \times AUMC_{0-\infty}[h^2 * IU/dL]}{AUC^2_{0-\infty}[h^2 * IU^2/dL^2]}$$

The **maximum concentration**, C_{max}, will be calculated as the maximum concentration post-infusion.

The **time to reach the maximum concentration**, T_{max}, in hours was defined as the time to reach C_{max}.

Incremental recovery (IR) in (IU/dL)/(IU VWF:RCo/kg) will be calculated as:

$$IR = \frac{C_{max}[IU/dL] - C_{pre-infusion}[IU/dL]}{dose\ per\ kg\ body\ weight\ [IU/kg]}$$

where C_{max} and $C_{pre\text{-}infusion}$ are the unadjusted concentration values.

The PK parameters AUC_{0-72h}/Dose, $AUC_{0-\infty}$/Dose, $AUMC_{0-\infty}$/Dose, MRT (mean residence time), CL (clearance), IR (incremental recovery), $T_{1/2}$ (elimination phase half-life), Vss (Volume of distribution at steady state), C_{max} (maximum concentration) and T_{max} (time to reach the maximum concentration) will be summarized by median and corresponding 90% confidence intervals, mean and corresponding 90% confidence intervals, standard deviation, Q1, Q3, IQR, geometric mean and corresponding 90% confidence intervals.

Descriptive statistics will be used to summarize VWF:RCo levels for each nominal time point on the PK curve.

PK analysis as described above will be carried out on the PKFAS as well as on the PKPPAS.

For all subjects in the PKFAS concentration vs. time curves will be prepared.

PK parameters will be derived using non-compartmental methods in WinNonlin.

The analysis will be performed on the FAS.

13.4.2.4 Safety

AEs that occurred during or after first IP infusion will be presented in summary tables. Summary tables shall indicate the number of subjects who experienced adverse events. Separate tables will be carried out for temporally associated adverse events; and for temporally associated or causally related adverse events.

In addition, tables will be prepared to list each AE, the number of subjects who experienced an AE at least once, and the rate of subjects with AE(s). AEs will be grouped by system organ class. Each event will then be divided into defined severity grades (mild, moderate, severe). The tables will also divide the AEs into those considered related (a "possibly related" or a "probably related" AE will be considered as a "related AE") to the treatment and those considered unrelated (an "unlikely related" or a "not related" AE will be considered as an "unrelated" AE). These tables will also be carried out for temporally associated adverse events; and for temporally associated or causally related adverse events.

All AEs; temporally associated AEs; causally related AEs; and temporally associated or causally related AEs will also be summarized by system organ class, preferred term, including the number of AEs, the number (%) of unique subjects, the frequency category (very common: ≥10%, common: ≥1% to <10%, uncommon: ≥0.1% to <1%, rare: ≥0.01% to <0.1%, very rare: <0.01%) and the number of IP-infusions associated with an AE.

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 infusion, irrespective of being related or not related to treatment.

AEs and SAEs for each subject, including the same event on several occasions, will be listed separately, giving both MedDRA preferred term and the original term used by the investigator, system organ class, severity grade, seriousness, relation to the treatment, onset date, and stop date.

AEs that occurred before first IP infusion will be listed separately.

Incidences of thrombotic events and severe allergic reactions will be listed. For the development of antibodies, proportions will be carried out.

The safety analyses will be based on the safety analysis set.

13.5 Exploratory Outcome Measures

[redacted]

13.6 Planned Interim Analysis of the Study

No formal interim analysis is planned for this study. However, a descriptive summary report for this study is planned after all subjects have completed at least 6 months of prophylactic treatment with rVWF.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Study Agreement. If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the Clinical Study Agreement.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable regulatory requirements as described in the Clinical Study Agreement. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

15.1.1 Investigator Report and Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the Clinical Study Agreement. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Clinical Study Agreement. Auditing processes specific to the study will be described in the auditing plan.

15.5 Non-Compliance with the Protocol

The investigator may deviate from the protocol to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor (Baxter) will also ensure the responsible ethics committee (EC) is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.6 Laboratory and Reader Standardization

A central laboratory/reader will be used for all clinical assessments except for pregancy testing and blood group test (refer to Section 12.9). Local laboratories are requested to provide their laboratory specifications of the individual tests that are also being tested locally.

16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the Clinical Study Agreement.

16.2 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the Clinical Study Agreement.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

16.3 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients and/or their legally authorized representative must sign an informed consent form before entering into the study according to applicable regulatory requirements and ICH GCP. An assent form may be provided and should be signed by patients less than 18 years of age. Before use, the informed consent form will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 16.2). The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable regulatory requirements. Patients or their legally-authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent form, patients or their legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised informed consent form, which have been approved by the applicable EC and regulatory authorities, will be provided by the investigator to the subjects who consented to participate in the study

16.4 Data Monitoring Committee

This study will be monitored by Data Monitoring Committee (DMC). The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. 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 stop a trial if it finds toxicities or if treatment is proven to be not beneficial. Details will be defined in the DMC charter.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the Clinical Study Agreement.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.8), records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

If electronic format CRFs are provided by the sponsor, only authorized study site personnel will record or change data on the CRFs. If data is not entered on the CRFs during the study visit the data will be recorded on paper and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (e.g., ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the Clinical Study Agreement.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the Clinical Study Agreement.

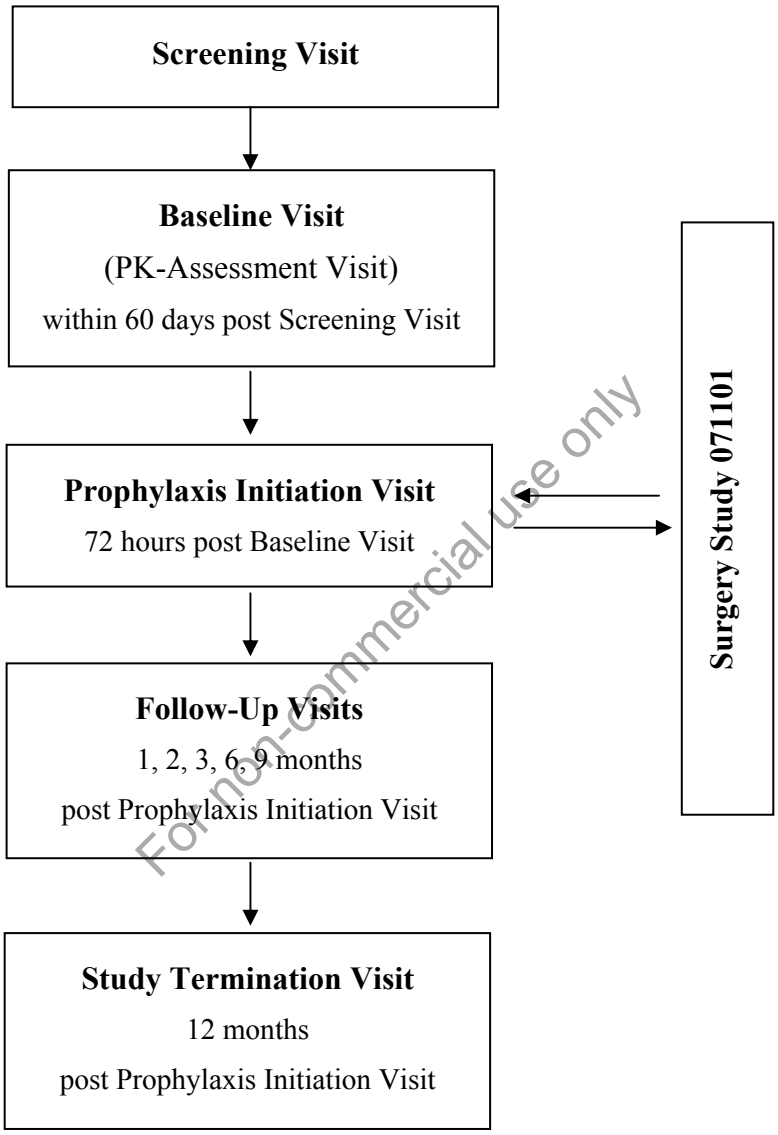
19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the Clinical Study Agreement.

20. SUPPLEMENTS

20.1 Study Flow Chart

Figure 1
Study Design for Baxter Clinical Study 071301



20.2 Schedule of Study Procedures and Assessments

Table 4
Schedule of Study Procedures and Assessments

Procedures/ Assessments	Screening Visit	Baseline Visit (PK-assessment visit)			Prophylaxis Initiation Visit	Interval/Follow-Up Study Visits					Study Completion/ Termination Visit
		Pre-infusion	Infusion	Post-infusion[g]		1 month± 1 Week	2 month± 1 Week	3 month± 2 Weeks	6 month± 2 Weeks	9 month± 2 Weeks	12 month± 2 Weeks
Informed Consent [a]	X										
Eligibility Criteria	X										
Medical History[b]	X	X									
Medications[c]	X	X			X	X	X	X	X	X	X
Non-drug Therapies[c]	X	X			X	X	X	X	X	X	X
Physical Exam	X	X			X	X	X	X	X	X	X
Adverse Events		X			X	X	X	X	X	X	X
Bleedings	X	X			X	X	X	X	X	X	X
Laboratories	X	X		X		X	X	X	X	X	X
Vital Signs[d]	X	X		X	X	X	X	X	X	X	X
ECG	X								X		X
IP Treatment[e]			X		X	X	X	X	X	X	X
IP Consumption/Treatment Compliance						X	X	X	X	X	X
Subject Diary					X	X	X	X	X	X	X
[redacted]	X[f]								X		X

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Continued

[a]) Occurs at enrollment (before screening).
[b]) Including documented history of on-demand and prophylactic treatment for the past 12 months and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 months
[c]) Including all medications and non- drug therapies taken in the 2 weeks prior to study entry and all the concomitant medications and non-drug therapies during the course of the study.
[d]) Vital signs (pulse rate, respiratory rate, and blood pressure): within 30 minutes before infusion start and 30 ± 15 minutes post-infusion.
[e]) IP treatment after the prophylactic treatment initiation visit at the site will be continued as home-treatment if the subject qualifies; a wash-out period of at least 72 hours is required after the last IP infusion before the follow-up visit. IP infusion will be given at the study site after the blood sample for immunology testing and IR determination is drawn.
[f]) Can be done either at the screening or the baseline visit.
[g]) Time points for blood draws post infusion: 30 ± 5 minutes; 60 ± 5 minutes; 6 ± 1 hours; 12 ± 1 hours; 24 ± 2 hours; 48 ± 2 hours; 72 ± 2 hours

20.3 Clinical Laboratory Assessments

Table 5.
Clinical Laboratory Assessment

Procedures/ Assessments	Screening Visit	Baseline Visit (PK-assessment visit)		Interval/Follow-Up Study Visits					Study Completion/ Termination Visit
		Pre-Infusion	Post-Infusion/ Prophyaxis Initiation Visit [k]	1 month± 1 Week	2 month± 1 Week	3 month± 2 Weeks	6 month± 2 Weeks	9 month± 2 Weeks	12 month± 2 Weeks
Hematology [a]	X	X	X	X	X	X	X	X	X
Clinical Chemistry [b]	X	X	X	X	X	X	X	X	X
Coagulation Panel/PK assessment[c]	X	X	X	X	X	X	X	X	X
Immunogenicity[d]	X	X	X[l]	X	X	X	X	X	X
Viral Serology[e]	X								
Urinalysis[f]	X								
VWD Gene Mutational Analysis / HLA genotype analysis and Analysis of VWF multimers [g]	X								
sP-selectin and D-dimer	X[h]								
Blood Group[i]	X								
Pregnancy Test[j]	X								
Exploratory Tests	X	X	X	X	X	X	X	X	X

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Continued

[a)] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. Hematology assessments during PK assessments will be determined prior IP infusion and 24±2 hours, 48±2 hours and 72±2 hours thereafter.

[b)] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin. Clinical chemistry will be determined at baseline, after 24±2 h, 48±2 hours and 72±2 hours during the PK assessments.

[c)] Coagulation panel/PK assessment: INR/aPTT, VWF:RCo, VWF:Ag, VWF:CB, FVIII:C, VWF Innovance (exploratory assay); during the PK assessment at the baseline visit blood samples will be drawn 30 min prior PK infusion; once the PK infusion is completed 30 ± 5 minutes; 60 ± 5 minutes; 6 hours ± 1 hour ; 12 ± 0.5 hours; 24 ± 2 hours, 48 ± 2 hours; 72 ± 2 hours and VWF:RCo, VWF:CB, VWF:Ag, VWF Ac, FVIII:C will be determined; in case of thrombotic event VWF multimers and ADAMTS13 will be analyzed to judge on a possibly relatedness to UHMW fractions of the IP.

[d)] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII – Inhibitory and Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG; .CD4* In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined. A washout period of at least 72 hours after the last IP infusion is required before blood samples for immunogenicity assessments can be drawn.

[e)] Viral Serology 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; HIV-1/HIV-2 Antibodies

[f)] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH

[g)] Not required if available in the subject's medical history; VWF multimers: additionally in case of thrombotic events

[h)] At screening and in case of thrombotic events

[i)] Blood group assessment major blood group (local laboratory) only if not available in the subject's medical history

[j)] Serum pregnancy test (in females of child-bearing potential if no urine sample is available)

[k)] The 72 h post-infusion laboratory assessments coincidence with the initiation visit for prophylactic treatment. After the blood samples are drawn for laboratory assessment for the 72 h post infusion PK assessment, the subject receives the first IP infusion for prophylactic treatment (prophylactic treatment initiation visit).

[l)] Only needed for subjects without PK assessment prior to their first IP infusion in this study.

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Link to Publisher´s Site:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003946.pdf

22. SUMMARY OF CHANGES

Not applicable.

INVESTIGATOR ACKNOWLEDGEMENT

RECOMBINANT VON WILLEBRAND FACTOR (rVWF)

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

CLINICAL TRIAL PHASE 3

ORIGINAL: 2014 FEB 19

OTHER PROTOCOL ID(s)

NCT Number: to be determined
EudraCT Number: to be determined
IND/IDE NUMBER: to be determined

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT

RECOMBINANT VON WILLEBRAND FACTOR (rVWF)

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

CLINICAL TRIAL PHASE 3

ORIGINAL: 2014 FEB 19

OTHER PROTOCOL ID(s)

NCT Number: to be determined
EudraCT Number: to be determined
IND/IDE NUMBER: to be determined

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
[redacted], MD
[redacted], Global Clinical Development

CLINICAL STUDY PROTOCOL

PRODUCT: Recombinant Von Willebrand Factor (rVWF)

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 SHORT TITLE: rVWF IN PROPHYLAXIS

PROTOCOL IDENTIFIER: 071301

CLINICAL TRIAL PHASE 3

AMENDMENT 1: 2016 APR 08

Replaces: ORIGINAL: 2014 FEB 19

OTHER ID(s)
NCT Number: to be determined
EudraCT Number: 2016-001478-14
IND NUMBER: to be determined

Study Sponsor(s):

Baxalta US Inc.
One Baxter Way
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1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted], Global Clinical Development
Baxalta US Inc.

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (e.g. investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) and suspected unexpected serious adverse events (SUSARs) to the ECs.

ALL SAEs, INCLUDING SUSARs, ARE TO BE REPORTED ON THE ADVERSE EVENT ELECTRONIC CASE REPORT FORM (eCRF) WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT. IF THE eCRF IS NOT AVAILABLE THEN THE SAE MUST BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR TO MEET THE 24 HOUR TIMELINE REQUIREMENT.

Bleeding events that meet seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) should be reported on the SAE eCRF or SAE Report form as an SAE.

Drug Safety contact information: see SAE Report form
Refer to SAE Protocol Sections and the study team roster for further information.

For definitions and information on the assessment of these events, refer to the following:

- AE, Section 12.1
- SAE, Section 12.1.1.1
- SUSARs, Section 12.1.1.2
- Assessment of AEs, Section 12.1.2

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	Recombinant von Willebrand factor (rVWF)
Name(s) of Active Ingredient(s)	Recombinant von Willebrand factor (rVWF)
CLINICAL CONDITION(S)/INDICATION(S)	
Subjects with severe von Willebrand disease (VWD) requiring prophylactic treatment with coagulation factor replacement	
PROTOCOL ID	071301
PROTOCOL TITLE	A prospective, phase 3, open label, international multicenter study on efficacy and safety of prophylaxis with rVWF in severe von willebrand disease
Short Title	rVWF in prophylaxis
STUDY PHASE	Ph3
PLANNED STUDY PERIOD	
Initiation	2016 JUN
Primary Completion	2018 Q1
Study Completion	2018 Q1
Duration	22 months
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
The purpose of this phase 3 study is to investigate the efficacy and safety, including immunogenicity and thrombogenicity, and [redacted] of prophylactic treatment with rVWF in subjects with severe VWD.	
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 and to compare it to the subject's historical ABR for spontaneous bleeding episodes during on-demand treatment.	
Secondary Objectives	
Secondary Objectives are • Additional efficacy assessments of prophylactic treatment • Safety and immunogenicity • Pharmacokinetics (PK) • Efficacy of the treatment of bleeding episodes	
Exploratory Objectives	
[redacted]	

STUDY DESIGN	
Study Type/ Classification/ Discipline	Efficacy and Safety
Control Type	No control
Study Indication Type	Prophylaxis and treatment of bleeding episodes
Intervention model	Single-group
Blinding/Masking	Open-label
Study Design	This is a phase 3, prospective, open-label, non-randomized, international multicenter study evaluating efficacy, safety, including immunogenicity and thrombogenicity, and [redacted] of prophylactic treatment regimen with rVWF for subjects with severe VWD. Subjects will be offered the option to continue to receive BAX111 in a long-term continuation study.
Planned Duration of Subject Participation	Approximately 15 months

Primary Outcome Measure

Efficacy

- Prospectively recorded ABR for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF and the subjects' historical ABR for spontaneous bleeding episodes during on-demand treatment.

Secondary Outcome Measure(s)

Efficacy

- Number (proportion) of subjects with reduction of ABR for spontaneous (not related to trauma) bleeding episodes during prophylaxis relative to the subjects' own historical ABR during on-demand treatment
- Number (proportion) of subjects with 0 bleeds during prophylactic treatment with rVWF
- Number of infusions and total weight adjusted consumption of rVWF and ADVATE (recombinant factor VIII/rFVIII) per month and per year during on-demand treatment

Safety

- Adverse events (AEs)
- Incidence of thromboembolic events
- Incidence of severe hypersensitivity reactions
- Development of neutralizing antibodies to VWF and FVIII
- Development of total binding antibodies to VWF and FVIII
- Development of antibodies to Chinese hamster ovary (CHO) proteins, mouse immunoglobulin G (IgG) and rFurin

Pharmacokinetic

- Incremental recovery (IR), terminal half-life ($T_{1/2}$), mean residence time (MRT), area under the curve/dose (AUC/dose), area under moment curve/dose (AUMC/dose), volume of distribution at steady state (Vss) and clearance (CL) based on Von Willebrand factor Ristocetin cofactor activity (VWF:RCo), Von Willebrand factor antigen (VWF:Ag), Von Willebrand collagen binding activity (VWF:CB) , INNOVANCE VWF Ac (exploratory assay) and time course (72 hours) of FVIII clotting activity (FVIII:C) levels.

Efficacy of the treatment of bleeding episodes • Number of infusions of rVWF and ADVATE (rFVIII) per spontaneous bleeding episode • Number of infusions of rVWF and ADVATE (rFVIII) per traumatic bleeding episode • Weight-adjusted consumption of rVWF and ADVATE (rFVIII) per spontaneous bleeding episode • Weight-adjusted consumption of rVWF and ADVATE (rFVIII) per traumatic bleeding episode • Overall hemostatic efficacy rating at resolution of bleed	
Exploratory Outcome Measures [redacted]	
INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**Dosage form**: lyophilized powder and solvent for solution for injection **Dosage frequency**: <u>Prophylactic Treatment</u> Subjects transitioning from on-demand treatment will be infused twice weekly with BAX 111 (rVWF) at doses of 50 ± 10 IU/kg rVWF:RCo. Dosage may be individualized within this range based on: • the PK data • type and severity of bleeding episodes the subject has experienced in the past • monitoring of appropriate clinical and laboratory measures Any further adjustment will have to be agreed with the sponsor in advance. <u>Treatment of Bleeding Episodes:</u> Dosage must be individualized based on the subject's weight, type and severity of bleeding episode and monitoring of appropriate clinical and laboratory measures. In general, an initial dose of 40-60 IU/kg VWF:RCo with 30-45 IU rFVIII [ADVATE]/kg) is recommended (rVWF:rFVIII ratio of 1.3:1: ± 0.2). In cases of major bleeding episodes, a dose of up to 80 IU/kg VWF:RCo may be infused. Subsequent doses, if necessary, will be administered with or without ADVATE to maintain VWF:RCo and FVIII levels for as long as deemed necessary by the investigator. **Mode of Administration:** intravenous
SUBJECT SELECTION	
Targeted Accrual	Approximately 18 subjects to achieve 15 evaluable subjects with severe VWD
Number of Groups/ Arms/ Cohorts	Single-group

Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding:
   a. Type 1 (VWF:RCo <20 IU/dL) or,
   b. Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2M or,
   c. Type 3 (VWF:Ag ≤3 IU/dL).
2. Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.
3. Subject currently receiving on-demand treatment for whom prophylactic treatment is recommended according to standard of care at the center.
4. Has ≥3 documented spontaneous bleeds requiring VWF treatment during the past 12 months
5. Availability of records to reliably evaluate type, frequency and treatment of bleeding episodes during 12 months of on-demand treatment prior to enrollment.
6. Subject is ≥18 years old at the time of screening and has a body mass index ≥15 but <40 kg/m^2.
7. If female of childbearing potential, subject presents with a negative blood/urine pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.
8. Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

Subjects who meet ANY of the following criteria are not eligible for this study:

1. The subject has been diagnosed with Type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD (e.g., qualitative and quantitative platelet disorders or elevated prothrombin time (PT)/international normalized ratio [INR] >1.4).
2. The subject has received prophylaxis treatment in the 12 months prior to screening (including those who received treatment once a month for menorrhagia but were not treated for any other bleeds).
3. The subject is currently receiving prophylaxis treatment.
4. The subject has a history or presence of a VWF inhibitor at screening.
5. The subject has a history or presence of a FVIII inhibitor with a titer ≥0.4 BU (by Nijmegen modified Bethesda assay) or ≥0.6 BU (by Bethesda assay).
6. The subject has a known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins.
7. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
8. The subject has a medical history of a thromboembolic event.
9. The subject is HIV positive with an absolute Helper T cell (CD4) count <200/mm^3.
10. The subject has been diagnosed with significant liver disease as evidenced by any of the following: serum alanine aminotransferase (ALT) 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).
11. The subject has been diagnosed with renal disease, with a serum creatinine level ≥2.5 mg/dL.
12. The subject has a platelet count <100,000/mL at screening.
13. The subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to signing the informed consent.

14. The subject is pregnant or lactating at the time of enrollment.
15. Patient has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
16. The subject has participated in another clinical study involving another investigational product (IP) or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
17. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
18. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
19. The subject has a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
20. The subject is in prison or compulsory detention by regulatory and/or juridical order
21. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.

Delay criteria

1. If the subject presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) the screening visit will be postponed until the subject has recovered.

STATISTICAL ANALYSIS

Sample Size Calculation

The determination of the sample size for this study is not based on strict statistical considerations. The sample size of a subset of at least 15 subjects with severe VWD, 5 of whom must have Type 3 VWD, is based on the Guideline on the Clinical Investigation of Human Plasma Derived von Willebrand Factor Products (CPMP/BPWG/220/02).[1]

Planned Statistical Analysis

Primary Outcome Measure:

The statistical analysis will provide descriptive summaries.

The prospectively recorded annualized bleeding rate (ABR) of spontaneous (not related to trauma) bleeding episodes during prophylactic treatment will be assessed using negative binomial distribution. Mean ABR of spontaneous bleeding episodes together with the corresponding 95% two-sided confidence intervals (CIs) will be reported for the prospective counts as well as those based on historical data.

Secondary Outcome Measures:

Efficacy:

For the number of infusions and for the total weight adjusted consumption of rVWF and ADVATE per month and per year during on-demand treatment for bleeding episodes, summary statistics will be carried out.

For the number (proportion) of subjects with reduction of ABR relative to historic ABR as well as for the number (proportion) of subjects with 0 bleeds, proportions and corresponding 95% two-sided CIs will be performed.

The cause, type, localization and severity of bleeding episodes will also be recorded and summarized.

Efficacy of the Treatment of Bleeding Episodes:

For the number of infusions of rVWF and ADVATE per bleeding episode, for the weight adjusted consumption of rVWF and ADVATE per bleeding episode as well as for the overall hemostatic efficacy rating at resolution of bleed, summary statistics will be carried out.

The severity and localization of bleeding episodes will also be recorded and summarized. Bleeding episodes should be organized by where they occur in addition to whether they occurred spontaneously or due to a traumatic event.

Pharmacokinetic:

The PK parameters AUC_{0-72h}/Dose, $AUC_{0-\infty}$/Dose, $AUMC_{0-\infty}$/Dose, MRT (mean residence time), CL (clearance), IR (incremental recovery), $T_{1/2}$ (elimination phase half-life), V_{ss} (Volume of distribution at steady state), C_{max} (maximum concentration) and T_{max} (time to reach the maximum concentration) will be summarized by mean, standard deviation and the corresponding 90% CIs, median, Q1, Q3, IQR and range.

Descriptive statistics will be used to summarize VWF:RCo levels for each nominal time point on the PK curve.

For all subjects concentration vs. time curves will be prepared.

Safety:

The number of subjects who experienced SAEs and the number of SAEs will be tabulated. In addition, the number of subjects who experienced AEs assessed as related to IP by the investigator and by the sponsor, and the number of IP-related AEs will be tabulated and subcategorized for thromboembolic events, neutralizing and total binding antibodies to VWF and FVIII, and hypersensitivity reactions by severity. Additionally, antibodies to Chinese hamster ovary (CHO) proteins, antibodies to mouse immunoglobulin G (IgG) and antibodies to rFurin.

A listing of all AEs will be presented by subject identifier, age, sex, preferred term and 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. An overview table for AEs will be provided, presenting the number of AEs, the number of subjects with AEs and the corresponding percent of subjects in total and by seriousness and relationship to study treatment. An additional summary table will present the total number of (mild, moderate, severe) AEs by system organ class and preferred term with relationship to IP.

<u>Exploratory Outcome Measures:</u>

[redacted]

4. TABLE OF CONTENTS

Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABR	Annualized bleeding rate
ADAMTS13	A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, number 13
AE	Adverse event
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC0-∞	Area under the plasma concentration /time curve from time 0 to infinity
AUC_{0-72h}/Dose	Area under the plasma concentration/time curve from time 0 to 72 hours post-infusion/dose
$AUC_{0-\infty}$/Dose	Area under the plasma concentration/time curve from time 0 to infinity/dose
AUC/Dose	Area under the curve/dose
AUMC	Area under moment curve
$AUMC_{0-\infty}$/Dose	Area under the first moment curve from time 0 to infinity/dose
aPTT	Activated partial thromboplastin time
B19V	Parvovirus B19
BILI	Bilirubin
BP	Blood pressure
BU	Bethesda Unit
BUN	Blood urea nitrogen
BW	Body weight
CAM	Cell adhesion molecule
CB	Collagen binding activity
CBC	Complete blood count
CD4	Helper T cell
CHO	Chinese hamster ovary
CI	Confidence interval
Cl	Chloride
CL	Clearance
C_{max}	Maximum plasma concentration
CR	Creatinine
CTA	Clinical Trial Agreement
eCRF	Electronic case report form
DMC	Data monitoring committee

Abbreviation	Definition
DIC	Disseminated intravascular coagulation
DVT	Deep vein thrombosis
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
FVIII	Factor VIII
FVIII:C	Factor VIII clotting activity
GCP	Good Clinical Practice
GI	Gastrointestinal
Glu	Glucose
GPIb	Glycoprotein Ib
HAMA	Human anti- mouse antibodies
HAV	Hepatitis A virus
HB	Hepatitis B
HBs	Hepatitis B surface
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
[redacted]	[redacted]
HRP	Horseradish peroxidase
IB	Investigator's brochure
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INR	International normalized ratio
IP	Investigational product
IQR	Interquartil range
IR	Incremental recovery

Abbreviation	Definition
i.v.	Intravenous
K	Potassium
k.o.	Knock out
LDH	Lactate Dehydrogenase
Na	Sodium
NMC	Non-medical complaint
NOAEL	No observed adverse effect level
MRI	Magnetic resonance imaging
MRT	Mean residence time
pdVWF	Plasma derived VWF product
pdVWF/FVIII	Plasma derived VWF product containing fractions of FVIII
PBAC	Pictorial Blood Assessment Chart
PCR	Polymerase Chain Reaction
PEF	Peak expiratory flow
PK	Pharmacokinetic
PKFAS	Pharmacokinetic Full Analysis Set
PKPPAS	Pharmacokinetic Per Protocol Analysis Set
PP	Per protocol
PT	Prothrombin time
Q1, Q3	Quartile
rFVIII	Recombinant factor VIII
rVWF	Recombinant von Willebrand factor
RBC	Red blood cell count
SAE	Serious adverse event
SAER	Serious adverse event report
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
[redacted]	[redacted]
SIC	Subject identification code
sP-selectin	Soluble P-selectin
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Elimination phase half life
TIA	Transient ischemic attack
Tmax	Time to reach the maximum concentration

Abbreviation	Definition
TTP	Thrombotic thrombocytopenic purpura
ULMW	Ultra-large molecular weight
ULN	Upper limit of normal
Vss	Volume of distribution at steady state
[redacted]	[redacted]
VTE	Venous thromboembolism (VTE)
VWD	von Willebrand disease
VWF	Von Willebrand factor
VWF:Ag	Von Willebrand factor antigen
VWF Ac	VWF activity measured INNOVANCE VWF Ac assay
VWF:CB	Von Willebrand Factor collagen binding
VWF:RCo	Von Willebrand factor: Ristocetin cofactor activity
WBC	White blood cell

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

Baxalta US Inc. (hereafter referred to as Baxalta or sponsor) has developed a human recombinant von Willebrand Factor (rVWF), which is co-expressed with recombinant factor VIII (rFVIII) in a Chinese hamster ovary (CHO) cell line and separated during the subsequent downstream process. To address concerns regarding the risk of transmission of blood-borne pathogens that may be introduced by human plasma, no exogenously added raw materials of human or animal origin are employed in the cell culture, purification, or formulation of the final container product. The only proteins present in the final container product other than rVWF are trace quantities of murine immunoglobulin (IgG, from the immunoaffinity purification), host cell (i.e., CHO) protein, rFurin (used to further process rVWF). rVWF is intended for the treatment of von Willebrand disease (VWD).

rVWF has been developed under the Baxalta internal code BAX111 and is used as investigational product (IP) in this study. rVWF may be used with or without ADVATE (rFVIII) for the treatment of bleeding episodes (see Section 8.7.4.4). See Section 8.7 for further information on the IPs and their usage in this study. A detailed description of rVWF is also provided in the Investigator's Brochure (IB).

rVWF was granted licensure in the United States in December 2015 under the brand name VONVENDI for the on-demand treatment and control of bleeding episodes in adults diagnosed with VWD; as of the date of this protocol VONVENDI is not yet available on the market.

6.2 Clinical Condition/Indication

Von Willebrand Factor (VWF) is a large multimeric glycoprotein with a molecular weight that varies from 500 to 20,000 kDa. VWF is normally found in plasma and produced in the alpha-granules of platelets and in endothelial cell organelles known as the Weibel-Palade bodies. VWF mediates platelet adhesion and aggregation at sites of vascular injury, one of the key functions in primary hemostasis. VWF also serves to stabilize coagulation factor VIII (FVIII), where FVIII is an essential cofactor of secondary hemostasis, which leads to fibrin clot formation.[2] Qualitative and/or quantitative deficiencies of VWF lead to a highly variable bleeding diathesis known as VWD, the most common of the hereditary coagulation factor deficiencies. Penetrance of VWD is highly variable, with only a small fraction of mildly affected patients displaying clinical symptoms or a family history of a bleeding diathesis.

The current biochemical-based classification distinguishes disorders arising from partial quantitative (type 1), qualitative (type 2), or virtually complete (type 3) deficiencies of VWF. Up to 70% of VWD patients are diagnosed with type 1 VWD, which may also be associated with minor functional defects in the molecule. In general, patients with type 1 VWD display mild clinical symptoms. Approximately 20 to 30% of VWD patients are diagnosed with type 2 VWD. Type 2 VWD is further divided into 4 subtypes (A, B, N, and M), reflecting distinct classes of functional abnormalities. These defects result in abnormal functional and/or multimeric distribution patterns that facilitate their diagnosis. The bleeding diathesis is usually moderate and primarily affects the mucosal tissues. Type 2N VWD patients are sometimes misdiagnosed as mild hemophilia A. Finally, approximately 1% percent of VWD patients exhibit a total or near total absence of VWF, which is classified as type 3 VWD. The incidence of type 3 VWD is estimated at 0.5-1.0 x 10^6. This type is also associated with a very low FVIII level (typically <5%) because the VWF carrier function for FVIII is lost. Replacement of VWF alone stabilizes endogenous FVIII, resulting in hemostatic levels within several hours post-infusion. Published results from studies of a plasma-derived VWF concentrate demonstrated an increase of FVIII at an approximate rate of 5.8 ± 1 IU dL^{-1} h^{-1}.[3] Type 3 VWD patients display severe hemorrhagic symptoms with bleeding predominantly in mucosal tissues, muscle and joints. All VWD patients, particularly those with type 2 or type 3 VWD, are at an increased risk for life-threatening bleeding episodes.

6.3 The role of prophylaxis in the management of VWD

The goals of long term prophylaxis in VWD are to maintain VWF and FVIII at sufficient levels to reduce the frequency and duration of bleeding episodes, the need for red blood cell transfusions, and the risk of complications, such as arthropathy.[4] In contrast to hemophilia, routine prophylaxis is not as established in VWD, although prophylaxis for patients with severe VWD have already been in use in Sweden during the 1950s.[5] In those early days of VWD treatment plasma FVIII concentrates containing VWF fractions were applied for replacement therapy, which then were followed by plasma derived VWF products containing fractions of FVIII (pdVWF/FVIII).

A Swedish cohort including 37 patients with type 3 VWD under prophylactic median treatment of 11 years (range 2 to 45 years) was retrospectively analyzed.[6;7] The doses used for prophylaxis, given once weekly for at least 45 weeks per year, were calculated based on 12 to 50 IU/kg body weight (BW) of FVIII clotting activity (FVIII:C) which approximately corresponded to 24-100 IU/kg von Willebrand factor: Ristocetin cofactor activity (VWF:RCo) considering that mainly Haemate with a known VWF:RCo/FVIII:C ratio of about 2 was used. An escalation of doses from 1 to 3 dose levels was allowed depending on the frequency and severity of bleeding episodes.

The results demonstrate that under long-term prophylaxis the number of bleeds could be reduced dramatically. Whereas the median value for bleeds per year was about 10 before prophylaxis this value could be reduced to less than 1 bleed per year during prophylaxis.

The benefit of prophylaxis for such indications was retrospectively also demonstrated in a cohort of Italian patients including type 3, 2A, 2M and type 1 patients. Prophylaxis was started after severe gastrointestinal or joint bleeding episodes and completely prevented bleeding episodes in 8 of these 11 patients and largely reduced the need of blood transfusions in the remaining 3. A regimen of 40 IU rVWF:RCo/kg was applied every other day or twice a week. A prospective study on prophylaxis, the PRO.WILL study, has been initiated in Italy.[8]

The results of a prospective study investigating the prophylaxis in children and young adults showed a significantly reduced bleeding frequency and bleeding score (3 vs. 0.07; 3 vs. 0. p<0.001) compared to the pre-prophylaxis values. The median dose was 40 (20-47) IU/kg VWF:RCo administered mainly twice weekly in 23 patients, 3 times a week in 7 patients and 4 times a week in 2 children.[9]

The VWD Prophylaxis Network initiated the VWD International Prophylaxis (VIP) trial to investigate the role of prophylaxis in patients with severe VWD including Type 1, 2, and 3. The dose of the factor replacement product was 50 IU /kgVWF:RCo. The frequency of the dose depended on the type of bleeding and could be increased from once weekly to twice weekly or 3 times per week. For the treatment of menorrhagia the dose of 50 IU/kg VWF:RCo was given on the first day of menses for 2 cycles. The frequency could be increased to Day 1 and 2 for 2 cycles or to Day 1, 2, and 3 of menses.

The study contains both retrospective and prospective study components. Results from the retrospective study component were published, including 61 subjects on prophylactic regimen in the past 6 months prior to enrollment or subjects with a history of prophylaxis over at least 6 month.[10] Differences in annualized bleeding rates (ABR) within individuals (during prophylaxis – before prophylaxis) were significant for those with primary indications of epistaxis (P = 0.0005), joint bleeding (P = 0.002) and gastrointestinal (GI) bleeding (P = 0.001). The difference in the group whose primary indication for treatment was abnormally heavy bleeding at menstruation (n = 4) was not significant (P = 0.25). The reduction of mucosal bleeding likely not only dependents on normal circulating levels of active VWF, but also on the presence of discrete concentrations of normal VWF inside the platelets and within endothelial matrices. The low subject number (n=4) and the treatment scheme for menorrhagia on Days 1, 2, and 3 of menses which might represent rather on-demand than prophylactic treatment may also account for the outcome in this study.

Results from the prospective study component were reported recently.[11] Eleven subjects completed the study. Six subjects had type 2A, and 5 subjects had type 3 VWD. Six subjects presented with epistaxis, 3 with GI bleeding, and 2 with joint bleeding. Seven subjects had dose escalation above the first level. Among the 10 subjects with evaluable bleeding log data, the use of prophylaxis decreased the median ABR from 25 to 6.1 (95% confidence interval [CI] of the rate difference: -51.6 to -1.7), and the median ABR was even lower (4.0; 95% CI: -57.5 to -5.3) when the subjects reached their final dosing level. The authors concluded that this was the first prospective study to demonstrate that prophylaxis with VWF concentrates is highly effective in reducing mucosal and joint bleeding rates in clinically severe VWD.

The results of the VIP study and previous investigations suggest that VWD patients with recurrent bleeding episodes and severe menorrhagia will benefit from a prophylactic VWF replacement therapy. There is evidence that up to 40% of patients with type 3 VWD experience joint bleeding which can lead to hemophilic arthropathy. Other potential indications for prophylaxis include patients with type 2A or 2B VWD with recurrent gastrointestinal bleeding, menorrhagia or frequent epistaxis.[4] Long-term prophylaxis for most patients with type 3 VWD and in some patients with type 1 or 2 VWD, depending on the pattern of bleeding, may be the treatment option of choice. Although the main experience with long-term prophylaxis is with secondary prophylaxis, primary prophylaxis starting at young age is recommended to prevent arthropathy in patients with severe VWD.[12]

However, further studies are needed to develop evidence-based guidelines for prophylactic treatment in VWD.

6.4 Population to be Studied

A total of approximately 18 eligible, adult subjects to achieve approximately 15 evaluable subjects with severe VWD are planned to be enrolled, of which a subset of at least 5 subjects will have type 3 VWD. Enrolled subjects (i.e., subjects who have signed the informed consent form) will be eligible to participate in the study if they meet all of the inclusion criteria (see Section 9.1) and none of the exclusion criteria (see Section 9.2).

6.5 Findings from Nonclinical and Clinical Studies

The following summarizes the key findings from relevant nonclinical studies as well as from the completed clinical studies **070701** (Phase 1 PK and safety in VWD), **071001** (Phase 3 safety and efficacy in the treatment of bleeding episodes in VWD), **071104** (Phase 1 safety and PK in hemophilia A), and **071401** (Phase 3, expanded access in a single subject with VWD). Potential risks and efficacy of rVWF:ADVATE are summarized in the following sections. For additional information on nonclinical and clinical Phase 1 results refer to the rVWF IB.

6.5.1 Findings from Nonclinical Studies

6.5.1.1 Primary Pharmacodynamics

Efficacy of rVWF combined with ADVATE was shown in VWD animal models, which have also low endogenous FVIII levels. Time to occlusion and stable thrombus formation was assessed in the carotid occlusion model in VWD mice. The results demonstrated that rVWF in combination with ADVATE acted efficiently in a dose-dependent manner and had higher efficacy than rVWF alone or plasma derived (pd)VWF. These results were confirmed in an additional study assessing blood loss and survival in a tail tip bleeding model in VWD mice. In a VWD dog rVWF stabilized canine FVIII in the circulation and significantly reduced the bleeding time.

6.5.1.2 Safety Pharmacology

The anaphylactoid and thrombogenic potential of the co-infusion of ADVATE and rVWF and the co-infused product's effects on blood pressure, cardiac and respiratory function and parameters of coagulation activation were investigated in 4 in vivo studies in different animal models. Safety pharmacology studies in rats, guinea pigs, rabbits, and dogs revealed no risks for anaphylactoid and thrombogenic potential of ADVATE in combination with rVWF. All observations in safety pharmacology studies are considered to lie within the biological variability of animal models or occurred due to known species-specific anaphylactoid effects of excipients.

6.5.1.3 Pharmacokinetics

Pharmacokinetic studies of both rVWF alone and combined with human rFVIII (rVWF+ADVATE) were conducted in VWD mice, VWD dogs, VWD pigs, rats, and cynomolgus monkeys. Human rVWF stabilized the endogenous FVIII in VWD mice, VWD pigs, and VWD dogs. Furthermore, the hypotheses that the area under the curve (AUC) with rVWF alone and rVWF+ADVATE is not inferior to the AUC with pdVWF (Haemate P) was tested and confirmed statistically in normal rats.

The pharmacokinetic (PK) characteristics of ADVATE were not affected by co-administration of rVWF in cynomolgus monkeys. The PK data in the FVIII knock out (k.o.) mice model are inconclusive and might not be relevant for the clinical situation. However, a stabilizing effect of VWF on FVIII could be shown in a double knock out model in a dose dependent manner.

6.5.1.4 Toxicology

Single dose toxicity studies were conducted in C57BL/6J-mice, VWD mice, rats, rabbits, and cynomolgus monkeys. Rats, rabbits, and cynomolgus monkeys showed no signs of toxicity. Signs of microthrombosis, an exaggerated pharmacological effect, were observed in mice. Mice are not capable of sufficiently cleaving the rVWF subunit as murine disintegrin and metalloproteinase with a thrombospondin type 1 motif, number 13 (ADAMTS13) does not decrease the ultra-large molecular weight multimers of rVWF.[13] The observed symptoms of microthrombosis are interpreted as a species-specific exaggerated pharmacological effect. Studies evaluating the safety of repeated administration of rVWF with or without ADVATE (daily over 14 days) were performed in a rodent (rat) and non-rodent (cynomolgus monkey) species. Reversible signs of exaggerated pharmacological effects (regenerative anemia, thrombocytopenia, and treatment-related histopathologic changes in the heart, liver, and spleen) were observed in rats that were administered 1400 U VWF:RCo/kg /day + 1080 IU ADVATE/kg/day intravenously once daily for 14 days. Also, these findings are interpreted as a species-specific exaggerated pharmacological effect due to the low susceptibility of human rVWF to cleavage by rodent ADAMTS13.[13] No toxicologically relevant changes were evident for clinical observations, body weight, feed consumption, ophthalmology, urinalysis, coagulation, and serum chemistry parameters, platelet aggregation, and gross pathology. rVWF combined with ADVATE was well tolerated in cynomolgus monkeys after daily intravenous (i.v.) (bolus) administration of 100 U VWF:RCo/kg rVWF combined with 77 IU/kg ADVATE over a period of 14 days. No adverse effects could be detected in this species. There were no signs of hemolysis, thrombosis, or thrombocytopenia after repeated intravenous application of rVWF with or without ADVATE. Therefore, 100 U VWF:RCo/kg/day rVWF with or without 77 IU/kg ADVATE was considered the no observed adverse effect level (NOAEL) in this study, which was the highest dose tested. Anti-drug antibodies, however, were formed in both species and resulted in a significant reduction in drug exposure after 14 applications as compared to a single application. These antibodies substantially reduced the systemic exposure to the test substance as compared to a single dose administration. No adverse effects due to antibody formation were observed in both species.

rVWF combined with ADVATE was well tolerated locally and no genotoxic potential was evident after 2 in vitro and 1 in vivo genotoxicity study. A study on the influence of co-administration of VWF and ADVATE on the immunogenicity of ADVATE in 3 different hemophilic mouse models (E17 hemophilic Balb/c mice, E17 hemophilic C57BL/6J mice, and E17 hemophilic human F8 transgenic mice) showed that rVWF does not negatively impact the immunogenicity of ADVATE in any of the three different hemophilic mouse models.

6.5.2 Findings from Clinical Studies

Two phase 1 studies with rVWF either alone or co-administrated with ADVATE in patients with VWD **070701** and Hemophilia A **071104** and 1 phase 3 study with rVWF in patients with VWD **071001** have been conducted and the results were analyzed and evaluated. Details on study design, populations enrolled, and safety and efficacy outcomes of these 2 phase 1 studies are presented in Section 6.5.2.1 and Section 6.5.2.2, and the phase 3 study in Section 6.5.2.3. Information on a single subject with VWD in Study **071401** is presented in Section 6.5.2.4.

Refer to rVWF IB for periodic updates from other rVWF studies.

6.5.2.1 Study 070701

Phase 1 clinical study **070701** was a multicenter, controlled, randomized, single-blind, prospective 3-step, dose escalation study to investigate safety, tolerability, and PK of rVWF combined at a fixed ratio with ADVATE (VWF:RCo/FVIII:C of 1.3 ± 0.2:1) in adults with severe VWD.[14] Subjects were enrolled in sequential cohorts in a dose escalating manner: Cohort 1, 2, and 3 received a single intravenous infusion of rVWF:ADVATE at the following doses: 2 IU/kg VWF:RCo (Cohort 1), 7.5 IU/kg VWF:RCo (Cohort 2), and 20 IU/kg VWF:RCo (Cohort 3). Subjects in Cohort 4 received a single intravenous infusion of rVWF:ADVATE and pdVWF/ADVATE at 50 IU/kg VWF:RCo in random order.

The primary endpoint was the tolerability and safety after single dose injections of rVWF:ADVATE at 2, 7.5, 20, and 50 IU/kg VWF:RCo for up to 30 days after the last IP infusion. The data generated in this phase 1 study suggest that rVWF:ADVATE up to the highest investigated dose of 50 IU/kg VWF:RCo is well tolerated and safe in adults with severe VWD. No thrombogenic risk or TTP-like syndrome was observed, and no neutralizing antibodies to VWF or FVIII were identified. There were no deaths or other serious adverse reactions, and no infusions were interrupted or stopped due to an AE.

Overall, the reported AE profile was similar between the recombinant and plasma-derived concentrates.

Secondary endpoints were the PK assessment of VWF:RCo, von Willebrand factor antigen (VWF:Ag) and multimeric composition of rVWF as well as FVIII:C at standardized time points after single injections of rVWF:ADVATE and pdVWF:FVIII.

The median VWF:RCo half-life ($T_{1/2}$) of rVWF at the 50 IU/kg dose was 16 hours. $T_{1/2}$ with pdVWF:FVIII at the same dose level appeared shorter at 12.58 hours, however, the limits of the 90% CI were similar (11.73 to 17.7 hours vs. 11.87 to 18.03 hours). The median half-lives of VWF:RCo were shorter with the lower investigated doses: 7.13 hours and 13.23 hours with the 7.5 IU/kg and 20 IU/kg doses, although these data were derived from a much smaller number of subjects.

In consequence of the missing ADAMTS13 cleavage, ultra-large molecular weight (ULMW) multimers are contained in the rVWF final product. The immediate cleavage of these ultra-large multimers by ADAMTS13 upon release into the circulation could be demonstrated applying sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE)/Immunoblot with polyclonal anti-VWF antibodies to detect the resulting rVWF subunit cleavage fragments.

Overall the data generated in this phase 1 study suggest that rVWF:ADVATE is well tolerated and safe in adults with severe VWD.

6.5.2.2 Study 071104

This study was a prospective, uncontrolled, non-randomized, multicenter proof of concept study to assess safety and PK of the addition of rVWF to ADVATE treatment in 12 evaluable subjects with severe hemophilia A. All subjects underwent 3 PK analyses: the first after infusion with ADVATE alone, the second after infusion with ADVATE plus 10 IU/kg rVWF and the third after infusion with ADVATE plus 50 IU/kg rVWF.

The PK analysis was performed at intervals of approximately 8 to 14 days. Before each infusion for PK assessment, there was a wash-out period of at least 5 days and the subjects were not actively bleeding.

Primary outcome measures indicate that co-administration of rVWF slightly sustain ADVATE activity with the highest observed ADVATE half-life of 13.74 h (CI 11.44 to 16.52) after co-infusion of 50 IU/kg ADVATE plus 50 IU/kg rVWF:RCo.

The highest improvement in ADVATE circulating half-life was observed in subjects with VWF:Ag levels below 100% which indicates an association between baseline VWF:Ag levels and ADVATE half-life increase.

No treatment related adverse events (AEs) or serious adverse events (SAEs) were reported. No subject withdrew due to an AE and there were no deaths. No binding antibodies to VWF, CHO, and rFurin were detectable in the confirmatory assay and no signs of a hypersensitivity to rVWF or ADVATE antigen were observed. Laboratory values over time did not indicate any potential safety risk for hemophilia A patients treated with rVWF and ADVATE in combination.

In summary, the data indicate that rVWF co-administered with ADVATE up to the highest dose of 50 IU/kg VWF:RCo is well tolerated and safe in hemophilia A patients.

6.5.2.3 Study 071001

This was a phase 3, multicenter, open-label, part-randomized clinical study to assess the PK, safety, and efficacy of rVWF:rFVIII and rVWF in the treatment of bleeding episodes in adult subjects with severe type 3 and severe non-type 3 VWD.[15] A total of 49 subjects were enrolled (signed informed consent) and screened, 18 subjects were randomized (Arm 1 and Arm 2 [PK 50] only), 37 subjects were treated with IP (all study arms), and 30 subjects completed the study.

The study consisted of 2 parts (Part A and Part B). Part A consisted of PK assessments alone (Arm 2: PK50 only [without treatment of bleeding episodes]), or PK assessments (Arm 1: PK50 and Arm 3: PK80) plus on-demand treatment period(s) of 6 months for bleeding episodes, or on-demand treatment for bleeding episodes only (Arm 4). Subjects receiving treatment for PK assessments and/or bleeding episodes in Part A were to be entered into Part B to continue on-demand treatment for bleeding episodes for 6 additional months for a total of 12 months in the study.

The primary outcome measure was the number of subjects with “treatment success” (extent of control of bleeding episodes), which was defined as a mean efficacy rating score of <2.5 for a subject’s IP-treated bleeding episodes during the study. The rate of subjects with treatment success was 100% (Clopper-Pearson exact 90% CI: 84.7 to 100.0) for bleeds where the assessments were made prospectively and excluding GI bleeds. Sensitivity analyses confirmed the results of the primary analysis.

Crossover results at 50 IU/kg VWF:RCo showed that the PK profile for rVWF VWF:RCo was independent of administration alone or with rFVIII (ADVATE) ($T_{1/2}$: 19.4 hours for rVWF and 16.6 hours for rVWF:rFVIII; IR: 1.8 U/dL per IU/kg infused for both rVWF and rVWF:rFVIII; MRT: 26.7 hours for rVWF and 25.2 hours for rVWF:rFVIII). FVIII levels increased substantially with a median peak at 24 hours of 111.0 U/dL for rVWF:rFVIII and 86.0 U/dL after rVWF alone, indicating that rVWF induces a sustained increase in endogenous FVIII activity. The rVWF PK profile was comparable at 50 IU/kg and 80 IU/kg VWF:RCo, and repeated PK at 80 IU/kg VWF:RCo showed close agreement between pretreatment and end-of-study results.

Further analysis of the PK data from the **071001** study supports the initial use of 50 IU/kg twice weekly for prophylaxis dosing in the present study for those subjects who are moving from on-demand to prophylaxis. Using 50 IU/kg for PK measurements, subjects in the **071001** study exhibiting a $T_{1/2}$ for rVWF of 14, 16, or 19 hours had BAX111 plasma concentrations at 72 hours after administration of 2.55, 4.01, and 6.49% above baseline, respectively, and plasma concentrations at 96 hours after administration of 0.78, 1.40, and 2.71% above baseline, respectively. Subjects who have significant spontaneous bleeding while on twice weekly prophylaxis will have their regimen increased to 50 IU/kg 3 times per week (see Section 8.7.4.2).

A total of 125 AEs occurred in 25/37 (67.7%) subjects (62/318 infusions [19.5%]) during or after infusion with IP. Of these, 116/125 were non-serious (all mild or moderate; none were severe), and 9 SAEs were reported in 7 subjects. Of 125 total AEs, 38 were temporally associated with IP; 8 AEs were considered causally related to IP: 6 non-serious related AEs (tachycardia, infusion site paraesthesia, electrocardiogram [ECG] t-wave inversion, dysgeusia, generalized pruritis, and hot flush) occurred in 4 subjects, and 2 related SAEs (chest discomfort and increased heart rate) occurred in 1 subject. No deaths occurred during this study.

None of the subjects developed anti-VWF or anti-FVIII neutralizing antibodies and no binding antibodies to VWF or rFurin, or antibodies against CHO protein or anti-Murine IgG were observed. No clinical or subclinical signs or symptoms of a thrombogenic event were observed in this study. Following an initial increase in ultralarge VWF multimers after administration of rVWF, a notable decrease in the proportion of large VWF multimers occurred between 12 and 24 hours post infusion, due to degradation by the endogenous ADAMTS13 followed by a continued decline until the end of the 96-hour follow-up period.

Overall, the data support the safe and effective use of rVWF with or without FVIII (ADVATE) in the treatment of bleeds in patients with VWD.

6.5.2.4 Study 071401: Single Subject with von Willebrand Disease

One subject who exhibited allergic reactions to currently marketed pdVWF products was treated in the single-subject study **071401** with rVWF only for the bleed treatment of continued hematuria, and for biopsy and surgical resection of a left-kidney mass.

For the initial rVWF infusion, the subject received a test dose of 5% of the total dose of 60 IU/kg rVWF:RCo at an infusion rate of 1 mL/min. After a 10 to 15-minute observation period, no adverse symptoms or signs were noted and the subject received the remaining 95% of the total dose. The subject was monitored for any signs of an allergic reaction, and none were noted. Treatment with rVWF every 12 to 24 hours was to continue at the discretion of the investigator based on VWF levels and clinical symptomatology. The subject had an excellent response and recovery, which allowed for daily dosing of rVWF and, within 24 hours, the subject's bleeding had stopped. Daily dosing of rVWF was maintained and the subject received his last dose on [redacted].

The subject also received rVWF for 7 days for prophylaxis for surgery (surgical resection of a left-kidney mass). The subject experienced no hemorrhagic complications and no AEs that were considered related to the use of rVWF.

6.6 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

Current treatment of VWD patients relies on desmopressin and VWF products manufactured from pooled human plasma. Human VWF produced by recombinant technology could offer a new perspective in treatment of VWD. The benefit for the individual subject is anticipated to be significant during this clinical study. He/she may benefit from a product that minimizes excessive FVIII administration. Variations in VWF multimeric composition may lead to variability with respect to treating or preventing bleeds in VWD subjects, especially mucosal bleeds which are especially problematic. rVWF product manufactured by Baxalta consistently contains ultra-large molecular weight (ULMW) VWF multimers due to the fact that the product has not been exposed to ADAMTS13. The initial presence of these ULMW VWF multimers, which are subsequently cleaved by the subject's endogenous ADAMTS13, may result in improved platelet and collagen binding and therefore provide more predictable treatment outcomes.

By using a recombinant product, the risk of contamination with blood derived viruses or variant Creutzfeldt-Jakob Disease associated with the use of products of human or animal origin has been virtually eliminated. At this stage of product development, the key societal benefit is a better understanding of advanced treatment options for VWD and enhanced product availability.

These benefits outweigh the following potential risks of rVWF:

- allergic-type hypersensitivity reactions as with any intravenous protein product
- the occurrence of thromboembolic events
- the development of neutralizing antibodies to VWF

Refer to the IB for further details on benefits and risks of the IP.

6.7 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives 2001/20/EC and 2005/28/EC, and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of this phase 3 study is to investigate the efficacy and safety, including immunogenicity and thrombogenicity, and [redacted] of prophylactic treatment with rVWF in subjects with severe VWD.

7.2 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 and to compare it to the subject's historical ABR for spontaneous bleeding episodes during on-demand treatment.

7.3 Secondary Objectives

Secondary Objectives are:

- Additional efficacy assessments of prophylactic treatment
- Safety and immunogenicity
- Pharmacokinetics
- Efficacy of the treatment of bleeding episodes

7.4 Exploratory Objectives

7.4.1 [redacted]

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

8. STUDY DESIGN

8.1 Brief Summary

8.2 Overall Study Design

This is a prospective, open label, uncontrolled, non-randomized, international, multicenter phase 3 study to evaluate efficacy, safety, including immunogenicity and thrombogenicity, and [redacted] of a prophylactic treatment regimen with rVWF in patients with severe VWD.

Subjects transitioning either from on-demand treatment or from prophylactic treatment will be infused twice weekly with BAX 111 (rVWF) at doses of 50 ± 10 IU/kg rVWF:RCo. The dose may be adjusted within this range based on the PK data, subject's history of bleeding episodes, and the results from clinical and laboratory assessments (see Section 8.7.4.2).

The overall duration of prophylactic treatment per subject will be 12 months.

During this period any bleeding episodes requiring substitution therapy with VWF concentrate to control bleeding will be treated with rVWF with or without ADVATE. The dose will be according to the bleeding severity and it will be adjusted to the clinical response (see Section 8.7.4.4.2).

The overall study design is illustrated in Figure 1.

8.3 Duration of Study Period(s) and Subject Participation

The overall duration of the study is approximately 22 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The subject participation period is approximately 15 months from enrollment to completion (i.e, last study visit), unless the subject is prematurely discontinued.

Subjects will be offered the option to continue to receive BAX111 in a long-term continuation study.

8.4 Outcome Measures

8.4.1 Primary Outcome Measure

The primary outcome measure is

- Efficacy:
  - Prospectively recorded ABR for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF and the subjects' historical ABR for spontaneous bleeding episodes during on-demand treatment.

8.4.2 Secondary Outcome Measures

8.4.2.1 Efficacy

- Number (proportion) of subjects with reduction of ABR for spontaneous (not related to trauma) bleeding episodes during prophylaxis relative to the subjects' own historical ABR during on-demand treatment
- Number (proportion) of subjects with 0 bleeds during prophylactic treatment with rVWF
- Number of infusions and total weight adjusted consumption of rVWF and ADVATE per month and per year during on-demand treatment

8.4.2.2 Safety

- AEs
- Incidence of thromboembolic events
- Incidence of severe hypersensitivity reactions
- Development of neutralizing antibodies to VWF and FVIII
- Development of total binding antibodies to VWF and FVIII
- Development of antibodies to Chinese hamster ovary (CHO) proteins, mouse immunoglobulin G (IgG) and rFurin

8.4.2.3 Pharmacokinetics

- Incremental recovery (IR), terminal half-life ($T_{1/2}$), mean residence time (MRT), area under the curve/dose (AUC/dose), area under moment curve/dose (AUMC/dose), volume of distribution at steady state (Vss) and clearance (CL) based on Von Willebrand factor Ristocetin cofactor activity (VWF:RCo), Von Willebrand factor antigen (VWF:Ag), Von Willebrand collagen binding activity (VWF:CB) , INNOVANCE VWF Ac (exploratory assay) and time course (72 hours) of FVIII clotting activity (FVIII:C) levels.

8.4.2.4 Efficacy of the Treatment of Bleeding Episodes

- Number of infusions of rVWF and ADVATE (rFVIII) per spontaneous bleeding episode
- Number of infusions of rVWF and ADVATE (rFVIII) per traumatic bleeding episode

- Weight-adjusted consumption of rVWF and ADVATE (rFVIII) per spontaneous bleeding episode
- Weight-adjusted consumption of rVWF and ADVATE (rFVIII) per traumatic bleeding episode
- Overall hemostatic efficacy rating at resolution of bleed

8.4.3 Exploratory Outcomes Measure

8.5 Randomization and Blinding

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

8.6 Study Stopping Rules

This study will be stopped if 1 or more of the following criteria are met:

1. Two subjects develop a thromboembolic event
2. Two subjects develop severe hypersensitivity reactions (e.g., clinically significant localized urticaria, generalized urticaria, wheezing, or anaphylaxis); or infusion related tightness of the chest or hypotension
3. Two subjects develop signs and symptoms, suggestive of a thrombotic thrombocytopenic purpura-like syndrome (subjects with type 2B VWD developing thrombocytopenia or changes of the platelet count as described below, will be evaluated on case by case, whether they need to be accounted for), such as
    - A drop in platelet count of 50% of subject's baseline or less than 100.000 per microliter
    - 3-fold increase in lactate dehydrogenase (LDH)
    - Impaired renal function as determined by:
        - Creatinine increase of 1.5-fold from baseline levels

- Blood urea nitrogen (BUN) increase from normal levels to a level > 60 mg/dL

4. Any subject has abnormal liver function:
   - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations >5 times upper limit of normal (ULN) in the absence of a concomitant bilirubin increase
   - ALT and/or AST elevations >3 times ULN in the presence of a total bilirubin increase >2 times ULN or an international normalized ratio (INR) >1.5 without findings of cholestasis or other alternate etiology to explain the elevations (i.e., "Hy's Law cases")
   - ALT and/or AST elevations >3 times ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
5. Two subjects develop rVWF neutralizing antibodies

The study may be stopped at any time by the sponsor.

The sponsor ultimately will decide whether to terminate, temporarily halt or modify the study based on the data monitoring committee (DMC) recommendation.

8.7 Investigational Product(s)

8.7.1 Packaging, Labeling, and Storage

8.7.1.1 rVWF (Recombinant von Willebrand Factor)

rVWF will be packaged in boxes with 2 glass vials, one containing the lyophilized rVWF, and the second vial containing the diluent. Further details are provided in the IB and Pharmacy Manual. The rVWF label will include, at a minimum, the actual VWF:RCo potency and the date of expiration.

rVWF should be refrigerated (2-8°C [36-46°F]) in lyophilized form. Deviations from the storage condition have to be communicated and followed up with the sponsor. Inadequately stored product will have to be placed in quarantine and may only be used after written investigational product administration authorization by the sponsor. After removal of the product from the refrigerator the product must not be returned to the refrigerator and has to be used immediately. rVWF must not be used beyond the expiration date printed on the vial. Avoid freezing at all times.

8.7.1.2 rFVIII (Recombinant Factor VIII /ADVATE)

ADVATE will be packaged in boxes with 2 glass vials, one containing the lyophilized rFVIII, and the second vial containing the diluent. Further details are provided in the IB and Pharmacy Manual. The ADVATE label will include, at a minimum, the actual FVIII:C potency and the date of expiration.

ADVATE should be refrigerated (2-8°C [36-46°F]) in powder form and should not be used beyond the expiration date printed on the vial. Deviations from the storage condition have to be communicated and followed up with the sponsor. Inadequately stored product will have to be placed in quarantine and may only be used after written investigational product administration authorization by the sponsor. After removal of the product from the refrigerator the product must not be returned to the refrigerator and has to be used immediately. Avoid freezing at all times.

8.7.2 Reconstitution

The reconstitution procedures for both rVWF and ADVATE products are detailed in the Pharmacy Manual.

8.7.3 Administration

Following reconstitution, rVWF and ADVATE (in case of bleeding episode treatment) should be administered to study subjects at room temperature and within 3 hours of reconstitution. The reconstituted rVWF and ADVATE, should be inspected for particulate matter and discoloration prior to administration, whenever the solution and container permit. The solution should be clear and colorless in appearance. If not, do not administer the product. Plastic syringes provided by the sponsor must be used since coagulation factors tend to stick to the surface of glass syringes.

Investigational product infusions should be given at a rate which should not exceed 4 mL/minute. The investigator/ subject shall ensure that no visible residual volume remains in the syringe(s) and that the complete content is administered. Upon completion of the infusion, the butterfly catheter should be flushed with at least 2 mL of saline solution. In case of a (central) venous access device, the flush should be with at least 10 mL of saline solution. The IP infusions should be administered over a duration of 2 to 15 minutes, depending on the volume.

Only the actual potencies of rVWF and ADVATE as stated on the vial labels and described in the Pharmacy Manual should be used. A variation of up to 10% of the intended dose for prophylactic infusions and of the intended dose for treatment of bleeding episodes is permissible and the exact dose should be recorded on the Case Report Form (CRF).

At study visits where recovery analysis is being done, vials with the same lot numbers should be used throughout the PK IP infusion per subject.

For treatment of bleeding episodes there are 2 options for the preparation of rVWF and ADVATE for infusion if needed.

Preferably sequential administration will be done: separate syringes of the appropriate dose of rVWF and ADVATE will be prepared for sequential infusion. rVWF should be infused first sequentially followed preferably within 10 minutes by infusion of ADVATE. Only the actual potencies of rVWF and ADVATE as stated on the vial labels and described in the Pharmacy Manual should be used.

Alternatively, premixed solutions can be administered: rVWF and ADVATE will be an i.v. admixture in a single syringe to achieve the appropriate dose. The contents of each vial of rVWF or ADVATE can be drawn into 1 syringe by using a separate unused reconstitution device as described in the Pharmacy Manual.

The final dose of rVWF:ADVATE should be at a ratio of 1.3:1 ± 0.2.

8.7.4 Description of Treatment

8.7.4.1 Baseline Visit (PK-Assessment Treatment)

The first IP infusion for PK assessment should be within 42 days after the completion of screening procedures and confirmation of eligibility.

At the baseline visit the subjects will receive a dose of 50 ± 5 IU/kg rVWF:RCo for PK assessment. Blood samples will be drawn within 30 minutes pre-infusion, and at 7 time points post-infusion (30 ± 5 minutes, 60 ± 5 minutes, 6 ± 1 hours, 12 ± 1 hours, 24 ± 2 hours, 48 ± 2 hours, 72 ± 2 hours).

Subjects previously enrolled in rVWF studies **070701** or **071001** and having previously undergone PK assessments in these studies are required to repeat the PK assessment due to different dose and time points used in these former studies (see Section 12.9.1 and Section 20.3). A washout period of at least 5 days is required prior to infusion of rVWF for PK assessment for subjects previously treated with rVWF.

Subjects who participated and had a major procedure performed in the surgery study **071101** will not need an additional PK assessment. Identical PK dose and time points are used for both studies **071101** and **071301**. Subjects who participated and had a minor procedure performed in the surgery study **071101** will need a PK assessment.

8.7.4.2 Prophylaxis Initiation Treatment

The prophylaxis initiation treatment visit will coincide with the 72 ± 2 h PK assessment. At this visit subjects will receive their prophylaxis initiation dose of 50 ± 10 IU/kg rVWF:RCo after the blood draw for the 72 ± 2 hours post-infusion PK assessment. If subjects do not need an additional PK assessment (e.g., subject has participated in the surgery study **071101** and had a major procedure performed), subjects must receive the IP for prophylaxis initiation treatment within 42 days after screening and confirmation of eligibility. The exact standard prophylaxis dose may range between 40 and 60 IU/kg based on:

- available historical PK data
- type and severity of bleeding episodes the subject has experienced in the past and
- monitoring of appropriate clinical and laboratory measures

Dose adjustments during the continued prophylactic treatment are described in Section 8.7.4.3.

The subject will be trained on IP reconstitution and administration and may then qualify for home treatment (see Section 8.7.4.3.2). Refer to Table 5 for study procedures and Table 6 for clinical laboratory assessments.

8.7.4.3 Prophylaxis Treatment

The standard prophylactic dose is 50 ± 10 IU/kg rVWF:RCo. All subjects will initially receive BAX111 (rVWF) twice per week (Table 1, Schedule A). Examples of all dosing schedules are provided in Table 1.

Table 1
rVWF Dosing Schedule Examples: Schedules, A, B, and C

Example	M	T	W	Th	F	Sat	Sun	M	T	W	Th	F	Sat	Sun
Schedule A	X			X				X			X			
Schedule B	X		X			X		X		X			X	

Dose and frequency adjustments will be agreed with the sponsor in advance unless it constitutes an urgent safety measure. Dose adjustments to higher doses (not exceeding the upper dose limit of 80 IU/kg rVWF:RCo) and adjustments to frequency will only be allowed in cases of persisting high bleeding rates due to insufficient therapeutic response.

8.7.4.3.1 Treatment escalation

Criteria for dose and frequency escalation are specific to each bleeding indication (Table 2) but, overall, involve 1 significant breakthrough bleeding episode despite compliant prophylaxis. Subjects entering the study will begin prophylaxis treatment according to Schedule A (Table 1) and will remain at this dose and frequency until meeting the criteria for escalation to the next higher schedule: for example, from 2 infusions of 50 ± 10 IU VWF:RCo/kg/week to 3 infusions of 50 ± 10 IU VWF:RCo/kg/week (Schedule B) to achieve adequate prophylaxis.

Table 2
Criteria for escalation specific to each bleeding indication

	Schedule A	Schedule B
Joint bleeding	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a spontaneous joint bleeding episode occurs while on this regimen, the subject will escalate to Schedule B following its resolution	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
GI bleeding	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a severe GI bleeding episode occurs while on this regimen, the subject will escalate to Schedule B following its resolution	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Menorrhagia	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) on days 1 and 2 of menses for 2 cycles. Menstrual flow will be monitored by the PBAC score. If the average pictorial chart score is > 185, then the subject will escalate to Schedule B	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) on days 1, 2, and 3 of menses. Menstrual flow will be monitored by the PBAC score.
Epistaxis	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. The subject will escalate to Schedule B in the event of 1 occurrence of breakthrough bleeding requiring intervention such as iron replacement therapy, transfusion, packing, hospitalization; or 2 bleeding events that require treatment with factor replacement	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.

Table 2
Criteria for escalation specific to each bleeding indication

	Schedule A	Schedule B
Oral and Other Mucosa	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. The subject will escalate to Schedule B in the event of 1 occurrence of breakthrough bleeding requiring intervention such as iron replacement therapy, transfusion, packing, hospitalization; or 2 bleeding events that require treatment with factor replacement.	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Muscle and Soft Tissue	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a spontaneous bleeding episode occurs while on this schedule, the subject will escalate to Schedule B following its resolution.	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.

GI: gastrointestinal; PBAC: Pictorial Blood Assessment Chart

Dose and frequency reduction will only be allowed in case plasma VWF or FVIII levels are exceeding the recommended ranges.

If a subject does not adequately respond to rVWF therapy, he/she will be evaluated for the presence of neutralizing and total binding anti-VWF antibodies (see Section 12.9.3.2).

If a subject experiences a bleed while receiving rVWF three times per week, the investigator should treat the bleed with rVWF at doses up to 80 IU VWF:RCo/kg at a frequency determined by the investigator until the bleed resolves. Upon resolution of the bleeding event, the subject will return to their assigned prophylaxis regimen.

It is essential for the success of this study that the subjects adhere to treatment regimens. Therefore, procedures for monitoring subject's compliance are implemented (see Section 10.7).

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. For example, a subject routinely infuses IP on Monday and Thursday, he/she misses the Monday time point and therefore may infuse the IP on the next day (Tuesday) and thereafter proceed with infusing the IP on Thursday (considering a minimum 12 hours between the infusions) and return to the initial schedule.

If more than 30% of infusions of IP are missed within the visit interval of 3 months the subject will be discontinued from the study (see Section 9.4).

8.7.4.3.2 General Instructions for Home Treatment for Prophylaxis

At the discretion of the investigator, a subject may be considered suitable for home treatment only after the subject has received at least 1 infusion of IP in the clinic, either during planned IP exposure (PK or prophylaxis) or during the treatment of bleeding episodes, and meets the following additional criteria:

1. Fully understands the concept of a clinical study and related documentation (documented training of at least 30 minutes),
2. Has a history of previous experience with home treatment including self-administration and treatment with VWF containing concentrates,
3. Has adequate time for initial training of the study drug preparation (preparation, mixing and infusion of the IP(s) (documented training of at least 30 minutes).

In the event a healthcare professional is required to administer IP, he/she must be trained and qualified by the sponsor on the above procedures prior to the decision for home treatment. A Subject Guideline detailing all instructions and information listed above will be provided to each subject.

8.7.4.4 Treatment of Bleeding Episodes

8.7.4.4.1 General Instructions for Home Treatment of Bleeding Episodes

If a subject experiences a bleeding episode, he/she should contact the study site immediately and the site investigator should provide instructions on the treatment regimen. If the subject initiates the treatment at home, he/she should at least follow up with the study site if a visit is needed as per the standard of care at the center.

In the event a healthcare professional is required to administer treatment at the subject's home, he/she must be trained and qualified by the site investigator on the above procedures prior to the decision for home treatment. Once a subject has received 1 infusion of rVWF in the clinic (either during planned IP exposure or during the treatment of a bleeding episode) and meets the criteria for home treatment, the treatment of bleeding episodes with IP can be conducted at home (see Section 8.7.4.3.2).

If a subject is not qualified for home treatment, rVWF infusions must be administered at the study site.

If a subject experiences a bleeding episode that requires treatment between the screening and the prophylaxis initiation visit, the subject will be treated with IP (rVWF with or without ADVATE). Treatment with IP must occur at the study site unless the subject has previously qualified for home treatment with rVWF. If rVWF treatment is not feasible, the subject may use his/her standard of care, such as commercial pdVWF/FVIII products. In any case a washout period of at least 5 days is required prior to rVWF PK infusion at the PK assessment visit.

If a subject experiences a bleeding episode requiring treatment during the PK assessment, rVWF will be used to treat the bleed. Blood draws for PK assessment will be stopped and the PK assessments will be repeated once the bleed has resolved and the subject is free of any symptoms related with the bleeding episode. Dose and frequency of rVWF infusions or any other replacement therapy to stop the bleed should be recorded in the e-CRF.

8.7.4.4.2 Dosing Recommendations for Treatment of Bleeding Episodes

If an acute bleeding episode occurs, the subject will be treated with rVWF with or without ADVATE. In general initially, an infusion of rVWF: ADVATE at an rVWF: ADVATE ratio of 1.3:1± 0.2 will be administered. Subsequent infusions may either use rVWF alone or with ADVATE, based on FVIII levels, if available.

If FVIII levels are not available, dosing is at the discretion of the investigator based upon the individual subject's PK data. Using ADVATE in addition to rVWF in subsequent doses carries the risk of an excessive rise in FVIII:C. Therefore, reduced doses of ADVATE and/or prolongation of the dose interval should be considered.

In general the aim of the initial dose should be full replacement of VWF with VWF:RCo levels of >0.6 IU/ml (60%) and FVIII:C of >0.4 IU/mL (40%). In major bleeding episodes, subsequent doses should keep the trough level of VWF:RCo >50% for 3 days and then as deemed necessary by the investigator for subsequent days. In moderate bleeding episodes, the dose and trough level may be reduced to >30% for as long as deemed necessary by the investigator. Treatment for minor bleeding episodes will generally consist of only 1 or 2 doses of rVWF IP.

If the VWF:RCo level is above 150%, a planned treatment should be delayed by at least 12 hours; if the VWF:RCo level is above 200%, a planned treatment should be delayed by at least 24 hours. In either case, a lower subsequent dose (e.g., 20 IU/kg VWF:RCo) may be appropriate.

Dosing recommendations are listed in Table 3.

Dosage must be individualized based on the subject's weight, VWD type, and the severity of the bleeding episode, as well as on monitoring of appropriate clinical and laboratory measures. In the phase 1 study **070701**, 1.0 IU/kg VWF:RCo raised the circulating level of VWF:RCo by 0.017 IU/mL (1.7 %). In the same study, the observed mean half-life for rVWF was 19.3 hours, with a standard deviation of 10.9 hours.

Table 3
rVWF:RCo Dosing Recommendations for the Treatment of Bleeding Episodes due to VWD

Classification of VWD	**Hemorrhage**	**Dosage (IU VWF:RCo/kg body weight)**
Type 1 • Severe (Baseline VWF:RCo activity typically <20%)	Minor (e.g., epistaxis, oral bleeding, menorrhagia*)	40 to 50 IU/kg (1 or 2 doses)
	Major (e.g., severe or refractory epistaxis, menorrhagia*, GI bleeding, CNS trauma, hemarthrosis, or traumatic hemorrhage)	Initial dose 50 to 75 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment
Type 2 (all variants) and Type 3	Minor (clinical indications above)	40 to 50 IU/kg (1 or 2 doses)
	Major (clinical indications above)	Initial dose of 60 to 80 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment

* Menorrhagia is defined as excessive bleeding during menstruation. A diagnosis of menorrhagia will be defined by a prospectively completed Pictorial Blood Assessment Chart (PBAC) score >185 and normal cervical cytology or requiring use of a VWF-containing concentrate for treatment of excessive menstrual bleeding for at least one menstrual cycle during the prior year.

Variances of up to 10% in dosing are permissible during treatment of bleeding episodes, but rounding to the nearest vial size should be avoided.

Subjects with non-neutralizing binding anti-VWF antibodies should initially be treated with a dose known to be efficacious based on the subject's medical treatment history which may differ from the recommendations provided in Table 3. Subjects should be monitored for lack of efficacy as well as for FVIII (mandatory), VWF:RCo (mandatory), and VWF:Ag (optional where testing is not available) levels after 3 to 6 hours. Re-dosing with rVWF in combination with ADVATE using the same (initial) dose and adaptation of the dosing frequency should be considered until cessation of the bleed, if the FVIII and/or VWF:RCo levels drop below 30%-50% depending on bleeding severity.

The number of subsequent infusions and the dosage levels prescribed will be determined by the investigator on the basis of the clinical severity, response to current therapy, available laboratory data, and the subject's historical treatment for similar bleeding episodes.

8.7.5 Investigational Product Accountability

The investigator will ensure that the IP(s) is stored as specified in the Pharmacy Manual and that the storage area is secured, with access limited to authorized study personnel. The investigator will maintain records that the IP(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. The IP(s) must be dispensed only at the study site or other suitable location (e.g., infusion center; home, as applicable per study design), as specified in the protocol (see Section 10). Records will be maintained that includes the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

8.8 Source Data

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

No data will be entered directly onto the CRF.

For additional information on study documentation and CRFs refer to Section 17.2. The use of subject diaries is described in Section 10.5.

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding
   a. Type 1 (VWF:RCo <20 IU/dL) or,
   b. Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2M or,
   c. Type 3 (VWF:Ag ≤3 IU/dL).
2. Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.
3. Subject currently receiving on-demand treatment for whom prophylactic treatment is recommended according to standard of care at the center.
4. Has ≥3 documented spontaneous bleeds requiring VWF treatment during the past 12 months
5. Availability of records to reliably evaluate type, frequency and treatment of bleeding episodes during 12 months of on-demand treatment prior to enrollment.
6. Subject is ≥18 years old at the time of screening and has a body mass index ≥15 but <40 kg/m^2.
7. If female of childbearing potential, subject presents with a negative blood/urine pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.
8. Subject is willing and able to comply with the requirements of the protocol.

9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

1. The subject has been diagnosed with Type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD (eg qualitative and quantitative platelet disorders or elevated PT/INR >1.4).
2. The subject has received prophylaxis treatment in the 12 months prior to screening (including those who received treatment once a month for menorrhagia but were not treated for any other bleeds).

3. The subject is currently receiving prophylaxis treatment.
4. The subject has a history or presence of a VWF inhibitor at screening.
5. The subject has a history or presence of a FVIII inhibitor with a titer ≥0.4 BU (by Nijmegen modified Bethesda assay) or ≥0.6 BU (by Bethesda assay).
6. The subject has a known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins.
7. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
8. The subject has a medical history of a thromboembolic event.
9. The subject is HIV positive with an absolute Helper T cell (CD4) count $<200/mm^3$.
10. The subject has been diagnosed with significant liver disease as evidenced by any of the following: serum ALT 5 times the ULN; hypoalbuminemia; portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).
11. The subject has been diagnosed with renal disease, with a serum creatinine level ≥2.5 mg/dL.
12. The subject has a platelet count <100,000/mL at screening.
13. The subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to signing the informed consent.
14. The subject is pregnant or lactating at the time of enrollment.
15. Patient has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
16. The subject has participated in another clinical study involving another IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
17. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
18. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.

19. The subject has a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
20. The subject is in prison or compulsory detention by regulatory and/or juridical order.
21. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.

9.3 Delay Criteria

1. If the subject has an acute bleeding episode or presents with an acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) the screening visit will be postponed until the subject has recovered.

9.4 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (i.e., reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the termination visit (including cases of withdraw or discontinuation) are described in Section 10.6 and Section 20.2.

Discontinuation (i.e., complete withdrawal from study participation) may be due to dropout (i.e., active discontinuation by subject) or loss to follow-up (i.e., discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also will be withdrawn from treatment or discontinued from further study participation for the following reasons:

1. The subject is scheduled for an extended treatment period >3 months with non-topical immunomodulating drugs other than anti-retroviral chemotherapy (e.g., α-interferon, corticosteroid agents [equivalent to hydrocortisone greater than 10 mg/day]) during the course of the study
2. Subjects with chronic hepatitis B or C develop ALT/AST levels exceeding 5 times the ULN for >1 month

3. Subjects who experience severe hypersensitivity reactions, e.g., anaphylaxis upon exposure to rVWF
4. Subjects who develop a neutralizing inhibitor to rVWF and/or ADVATE (biological assays)
5. Subjects who demonstrate clinical signs of thromboembolic events
6. The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through completion of the pregnancy and up to 1 year post delivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome.
7. The subject begins lactating. IP exposure will be discontinued. The investigator will record a narrative description of the course of the baby's development.
8. The subject is not compliant with the prophylactic treatment regimen and does not adhere to the frequency of IP administration. Once ≥30% of infusions are missed within a visit interval (3 months), the subject will be discontinued from further participation in the study.

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient who provides informed consent (i.e., signs and dates the informed consent form) is considered a subject in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (e.g., 090701) to be provided by the sponsor, 2- or 3-digit number study site number (e.g., 02) to be provided by the sponsor, and 3- or 4-digit subject number (e.g., 0003) reflecting the order of enrollment (i.e., signing the informed consent form). For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 090701-020003. All study documents (e.g., CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The study site is responsible for maintaining a screening log that includes all subjects who provided informed consent. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

The overall study design is illustrated in the Figure 1. Details on the procedures to be performed at each study visit, including screening, are provided in Supplement 20.2 Schedule of Study Procedures and Assessments and Supplement 20.3 Clinical Laboratory Assessments.

10.3.1 Screening Visit

Written informed consent must be obtained from each subject before any study related procedures are performed. To initiate screening procedures, at least 72 hours must have elapsed since the last VWF administration and the subject must not be actively bleeding at the time of screening. Multimer analysis and VWD gene mutation analysis should be performed at screening if not available in the subject's medical history. The screening visit will be delayed if the subjects presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like symptoms, inflammatory diseases) until the event has resolved. All screening procedures and confirmation of eligibility shall take

place within 42 days prior to the first infusion of IP for PK assessments. If the IP is not infused within 42 days, all screening assessments except blood group, human leucocyte antigen (HLA), genetics, multimeric pattern and [redacted], must be repeated to reconfirm eligibility. Refer to Supplement 20.2 and Supplement 20.3. Upon completion of screening procedures, subject eligibility will be confirmed by the sponsor on a subject eligibility form before additional study procedures are undertaken. The subject will maintain a diary that will include infusion logs (see Section 10.5). The allocation of IP will be initiated after the subject has qualified for home treatment (see Section 8.7.4.3.2).

In the event of a subject experiencing a bleeding episode that requires treatment between the screening visit and the baseline visit (PK assessment visit), the subject will be treated with rVWF. If rVWF is not available for any reason, e.g., subject not yet trained on IP administration, study site visit for IP administration not feasible, etc., the subject may use his/her standard of care, such as commercial pdVWF/FVIII products.

10.3.2 Baseline Visit - PK-Assessment Visit

After screening and confirmation of eligibility each subject will undergo a PK assessment. Subjects who participated in the surgery study **071101** will not need to undergo a PK baseline assessment again if they had a major procedure performed, provided valid PK data from **071101** is available. These subjects may proceed directly with the prophylaxis initiation visit (refer to Section 10.3.3). All subjects will receive a dose of 50 ± 5 IU/kg rVWF:RCo to determine VWF and FVIII levels. Blood samples will be drawn within 30 minutes pre-infusion, and at 7 time points post-infusion (30 ± 5 minutes, 60 ± 5 minutes, 6 ± 1 hours, 12 ± 1 hours, 24 ± 2 hours, 48 ± 2 hours, 72 ± 2 hours). Refer to Section 20.2 and Section 20.3. IP infusion vials from the same lot number should be used for all PK-assessments per subject. Samples for measurement of FVIII and VWF activity taken through to 6 hours post-infusion will be obtained from an extremity different from that used for the infusion of IP. Where needed, the phlebotomy site will be kept patent via an infusion of normal saline. In this event, at least 5 mL of blood will be collected and discarded before collection of the next test sample into a fresh syringe.

If the subject has a central venous catheter, the central line should be used to administer the infusion and a peripheral venipuncture should be used to collect the blood samples. In the event that a blood sample must be drawn through the central line used for administration of IP, the line must first be flushed with at least 10 mL normal saline or other suitable catheter flush solution that does not contain anticoagulant. At least 5 mL of whole blood must be collected and discarded prior to obtaining the sample.

If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.7.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment.

10.3.3 Prophylaxis Initiation Visit

After the blood sample for the 72 hour PK assessment is drawn the subject will receive the first rVWF prophylactic dose of 50 ± 10 IU/kg rVWF: RCo. Details on dose are provided in Section 8.7.4.3.

If a subject did not undergo PK assessment (for example the subject has participated in the surgery study **071101** and has undergone PK in Study **071101** and had a major procedure performed, refer to Section 8.7.4.2), procedures and assessments at this visit include: adverse events, bleeding episodes, medications taken, non-drug therapies and laboratory assessment. Independent of previous PK assessment visits, within 2 hours prior the IP infusion, a physical examination will be performed. Vital signs will be assessed within 30 minutes prior to IP rVWF infusion and 30 minutes ± 15 minutes after IP infusion. For subjects with a previous PK assessment in the course of the surgery study, incremental recovery (IR) will be determined based on VWF: RCo activity assessed prior and after IP infusion. Further details are provided in Supplement 20.2 and Supplement 20.3.

10.3.4 Treatment of Bleeding Episodes

Treatment of bleeding episodes is described in detail in Section 8.7.4.4.

10.3.5 Follow-Up Visits (1 Month ± 1 Week, 2 Months ± 1 Week, 3 Months ± 2 Weeks, 6 Months ± 2 Weeks, 9 Months ± 2 Weeks)

Visits will be performed after the prophylaxis initiation visit at 1 month ± 1 week, 2 months ± 1 week, and 3 months ± 2 weeks and thereafter every three months ± 2 weeks. Additional visits may occur if clinically indicated (see Section 10.3.6).

When possible, site visits should be scheduled on days when the subject is expected to infuse BAX111. Within 2 hours prior to the rVWF IP infusion , a physical examination will be performed. Vital signs will be assessed within 30 minutes prior to IP infusion and 30 minutes ± 15 minutes after IP infusion. Incremental recovery (IR) will be determined at each follow-up visit based on VWF:RCo activity assessed prior to and after IP infusion.

The blood sample for IR analysis will be drawn within 30 minutes prior to IP infusion and 30 minutes ± 5 minutes after IP infusion. rVWF will be infused at the regular prophylactic dose, i.e., 50 ± 10 IU/kg rVWF:RCo. For each subject's recovery analysis IP infusion, vials from the same lot number should be used.

Testing for VWF:RCo VWF:CB, rVWF:Ag, INNOVANCE VWF:Ac (exploratory) and FVIII:C level will be performed using the blood sample obtained before and after IP infusion.

The blood sample prior to IP infusion will also be used for the assessment of neutralizing and binding antibodies, clinical chemistry and hematology. A washout period of at least 72 hours after the last infusion applies before the blood draw for the immunogenicity assays. Bleeding episodes and the hemostatic efficacy will be evaluated based on the review of the patient diary. Refer to Section 20.2 and Section 20.3. The evaluation of IP consumption and treatment compliance will be performed based on subject's diary entries. If a subject is not compliant with the prophylactic treatment regimen and does not adhere to the required frequency of administration of IP infusions (>30% of infusions were missed within a visit interval [3 months]) the subject will be withdrawn from the study.

At the 6 months ± 2 week visit an electrocardiogram (ECG) will be performed and [redacted] data will be collected.

For the hemostatic efficacy assessment the following information will be recorded by the subject in the patient diary: bleeding location, type, severity, onset and resolution date and time, infusion date and time, clinical efficacy according to the rating scale. If at any time during the study a subject's bleeding episode does not adequately respond to rVWF therapy, he/she will be evaluated for the presence of neutralizing and total binding antibodies. Refer to Section 12.9.3.2.

Further guidance on completing the subject's diary will be provided to the subjects during training for home treatment (see Section 8.7.4.3.2).

10.3.6 Unscheduled Visits

For any unscheduled visit (except for collection of IP) a clinical assessment will be performed as per the scheduled follow-up visits with the exception of [redacted], ECG, and IR determination (refer to Supplement 20.2 and Supplement 20.3).

Subjects who have more than one bleeding episode in 3 months, or an increased frequency of bleeding, should go to the study site for an unscheduled visit.

Follow-up visits after the subject has experienced a bleed may be requested by the investigator. Additional assessments may be required which are at the discretion of the investigator.

10.3.7 Study Termination Visit (12 months ± 2 weeks)

At the 12 month ± 2 week visit, a full PK analysis, as per the baseline PK assessment, will be performed. Blood samples will be drawn within 30 minutes pre-infusion, and at 7 time points post-infusion (30 ± 5 minutes, 60 ± 5 minutes, 6 ± 1 hours, 12 ± 1 hours, 24 ± 2 hours, 48 ± 2 hours, 72 ± 2 hours). If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.7.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment.

The following parameters will be used as part of the PK assessment:

- Incremental recovery of VWF:RCo, VWF:Ag, VWF:CB, and INNOVANCE VWF Ac (exploratory assay)
- AUC/dose, area under moment curve (AUMC/dose, clearance (CL), Volume of distribution at steady state (V_{ss}), mean residence time (MRT), of VWF:RCo ,VWF:Ag, VWF:CB, and INNOVANCE VWF Ac (exploratory assay)
- Half-life of VWF:RCo, VWF:Ag, VWF:CB, and INNOVANCE VWF Ac (exploratory assay)
- Time course of the FVIII:C levels
- VWF collagen binding (VWF:CB) levels

Refer to Supplement 20.2 and Supplement 20.3 for the other assessments to be performed at the PK assessment and study completion visits.

A washout period of at least 72 hours is required between the PK infusion and the study termination visit (at the time of the 72 hour postinfusion PK assessment).

Refer to Supplement 20.2 and Supplement 20.3 for the list of assessments to be performed at the termination visit.

Subjects will be offered the option to continue to receive BAX111 in a long-term continuation study.

10.4 Medications and Non-Drug Therapies

The following medications and non-drug therapies are **not** permitted within 30 days before study entry and during the course of the study:

Medications:

- 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) and an extended treatment period >3 months.
- Another investigational and/or interventional study drug (except rVWF and FVIII administered under the surgery protocol).

A subject who has taken any of these medications or received any of these non-drug therapies during the study will be withdrawn from the study.

The following medications are permitted during the course of the study:

- Antifibrinolytics (e.g., tranexamic acid, ε-amino caproic acid) or topical hemostats as needed, according to each institution's standard of care
- Emergent use of a VWF concentrate other than rVWF may be permissible under certain circumstances (see Section 8.7.4.4.1)

Details of all adjunctive hemostatic medication used, including dose and reason for use, will be recorded in the electronic Case Report Form (eCRF).

10.5 Subject Diary

1. An electronic subject diary will be provided to each subject at the baseline visit to record the following information:
    - IP infusions to include date, start and stop times of the infusion, number of vials utilized, and infusion volume for prophylactic treatment or treatment of spontaneous and traumatic bleeding episodes
2. Details of bleeding episodes (site and type of bleeding) and response to treatment as described in Section 8.7.4.4
3. Subjective hemostatic efficacy assessments.

Subjects and/or their legally authorized representatives will be trained on use of the diary. The diary will be provided in electronic format and remain with the subject for the duration of the study. The investigator will review the diary for completeness and request missing information periodically and in a timely manner.

Infusions performed at the study site will be recorded in the site's source documents and not in the patient diary.

Subject entries in the diary will serve as source records. During study participation the investigator has access to the database holding the subject diary data. After study closure, the investigator will receive the diary records for their subjects, including audit trail records, in PDF format. The data will be transmitted to the CRF by a validated transfer.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have completed all study procedures according with the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, AE (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, e.g., technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the study termination visit. If the termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the termination visit. If a subject terminates participation in the study and does not return for termination visit, his/her last recorded assessments shall remain with the last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.2 Schedule of Study Procedures and Assessments and Supplement 20.3 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

10.7 Procedures for Monitoring Subject Compliance

Subject compliance with the procedures of this study (treatment regimens and study visits) will be monitored by the investigator or/a licensed healthcare professional at the study site.

During the regular scheduled follow-up visits a direct review of the subject's source data (e-diaries) will be performed at the sites and evaluated against the protocol requirements. In addition drug accountability will be evaluated at each follow-up study visit and the study termination visit by comparing the infusions recorded in the subject diary with empty vials returned by each subject to the study site, and the study site's dispensing record. Protocol deviations will be noted in the final report.

11. ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

11.1 Assessment of Spontaneous Bleeding Episodes/Annualized Bleed Rate

The annualized bleed rate (ABR) will be assessed based upon each individual spontaneous bleed, requiring coagulation factor replacement therapy, i.e., rVWF treatment. The following details on bleeding episodes will be recorded by the subject in the electronic diary (for home treatment), the subject's healthcare provider in the site's source documents (for treatments away from the primary investigative site), or by authorized, qualified personnel at the participating site in the subject's medical records (for hospital-based treatment):

- Location of bleed; i.e., joint, menorrhagia, epistaxis, gastrointestinal, soft tissue, muscle, body cavity, intracranial, etc.
- Type of bleed; i.e., spontaneous, traumatic, unknown
- Severity of bleed; i.e., minor, moderate, and major (see Table 3)
- Date and time of onset of bleed
- Date and time of each infusion of rVWF or rVWF-ADVATE used to treat a bleeding episode
- Date and time of resolution of the bleeding episode

Study site personnel are qualified after they have undergone training during the qualification of the site.

All types of bleeds, including traumatic bleeds, will be recorded. Bleeding episodes should be organized by where they occur in addition to whether they occurred spontaneously or due to a traumatic event.

Bleeds occurring at the same anatomical location (e.g., right knee) with the same etiology (i.e., spontaneous versus injury) within 24 hours after onset of the first bleed will be considered a single bleed. Bleeding occurring at multiple locations related to the same injury (e.g., knee and ankle bleeds following a fall) will be counted as a single bleeding episode.

All efforts should be made to use rVWF for treatment of bleeding episodes. If needed, the use of a VWF concentrate other than IP for the treatment of bleeding episodes will not disqualify the subject from further participation in the study.

11.2 Evaluation of ABR before rVWF Prophylaxis and ABR under rVWF prophylactic treatment

At screening, the subject's medical history will be recorded, including the number of all spontaneous and traumatic bleeding episodes within the past 12 months. The maximum interval of bleed-free periods as well as trauma induced bleeding episodes will also be recorded (prospectively and retrospectively).

11.3 Number of Infusions and Total Weight Adjusted Consumption of rVWF and ADVATE

The number of rVWF and ADVATE (in case of bleeding episode treatment) infusions will be logged in the subject diary. Based on these entries the weight adjusted consumption will be calculated per month and per year.

11.4 Assessment of Efficacy for Treatment of Bleeding Episode

Investigators will be asked to assess and record hemostatic efficacy after resolution of each bleeding episode using the 4-scale rating system outlined in Table 4.

Table 4
Efficacy Rating Scale

Rating	Efficacy Rating Criterion	
	Minor and Moderate Bleeding Events	**Major Bleeding Events**
Excellent (=1)	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF containing coagulation factor containing product required	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF containing coagulation factor containing product required
Good (=2)	1-2 infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required	< 1.5 x infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required
Moderate (=3)	3 or more infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required	≥ 1.5 x infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required
None (=4)	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF containing coagulation factor containing product required	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF containing coagulation factor containing product required

11.5 Pharmacokinetic Assessment

Details on pharmacokinetic assessments are provided in Section 12.9.1.

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

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, whether or not considered causally related to the IP.

12.1.1.1 Serious Adverse Event

An SAE is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
    - Reviewed and confirmed seroconversion for human immunodeficiency virus
      (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)

- Development of neutralizing VWF antibodies
- Development of neutralizing antibodies to FVIII (titer ≥0.4 BU [by Nijmegen- modified Bethesda assay] or ≥0.6 BU [by Bethesda assay])
- Thromboembolic events (e.g., myocardial infarction, stroke, transient ischemic attack [TIA], deep vein thrombosis [DVT] or pulmonary embolism)
- Anaphylaxis (for definition, refer to Section 12.6.2) or severe hypersensitivity reactions

Uncomplicated pregnancies, following maternal or paternal exposure to IP are not considered an (S)AE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE.

12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any suspected adverse reaction to study treatment (i.e., including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following:

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment

Once determined to meet the criteria for a SUSAR, an SAE should be submitted to regulatory agencies expeditiously.

12.1.1.3 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet the criteria of an SAE.

12.1.1.4 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (e.g., IB, package insert). “Unexpected” also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.1.1.5 Preexisting Disease

Preexisting diseases that are present before entry in to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described on the AE CRF.

12.1.2 Assessment of Adverse Events

For the purposes of this study, the following will not be considered as AEs and will not be included in the analysis of AEs.

- Bleeding episodes are part of the underlying disease and therefore are not AEs; they will be evaluated in the context of efficacy.
  - For non-serious bleeding episodes caused by an injury, the injury would not be reported as an AE, unless it resulted in a medical finding other than a bleeding episode (e.g., abrasion of skin). Therefore, any VWD-related bleeding event (e.g., epistaxis, gastrointestinal bleeding, musculo-skeletal bleeding, menorrhagia) that is non-serious will not be reported as an AE. However, the investigator may decide that the event is an AE if the event also would have occurred in a healthy individual under the same circumstances.
  - For SAEs: Bleeding events that meet seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) should be reported on the SAE eCRF or SAE Report form as an SAE.
- Seroconversion after documented HAV/HBV vaccination prior to or during the study period.

Each AE from the first IP exposure to the study completion date will be described on the AE CRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2

For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution.

If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the protocol-specified dosage (including underdosing /overdosing [<20 IU/kg rVWF:RCo or >100 rVWF:RCo], abuse, and withdrawal, treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after administration of IP will be reported on a Pregnancy Form and followed-up at 1 year post-delivery, if feasible.

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the SAE Form within 24 hours after awareness: no additional reporting on CRFs is necessary.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.

- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, e.g., assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).
- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of IP
  - An alternative etiology is equally or less likely compared to the potential relationship to the IP
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:

- Reappearance of a similar reaction upon re-administration (positive re-challenge)
- Positive results in a drug sensitivity test (skin test, etc.)
- Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid

➢ Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within 5 days after IP infusion, the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

12.1.2.3 Safety Reporting

Adverse events/SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Table 5) and Section 12.1.2.

Adverse Events/SAEs are to be recorded on the AE page of the eCRF. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the investigational product, must be reported immediately (within 24 hours of the study center's first knowledge of the event). All SAEs must be reported via the Electronic Data Capture (EDC) system by completing the relevant eCRF page(s) in English. For instances in which the EDC may become unavailable, SAEs must be reported using the back-up paper SAE report (SAER) form to meet the 24-hour timeline requirement (for contacts and instructions refer to the SAER form). Once the EDC becomes available, the site must enter all SAE data as reported on the back-up paper SAER form on the applicable eCRF pages.

The initial SAE information reported on the applicable eCRF pages (or back-up SAER Form, if applicable) must at least include the following:

1. Protocol Number
2. Subject identification number and demographics (gender, age at onset of event and/or date of birth)
3. Investigational product exposure
4. Medical Term for Event (Diagnosis preferably)

5. Description of the (S)AE, including:
    - Date of onset
    - (S)AE treatment (drug, dose, route of administration)
    - Causal relationship by the Investigator
    - Measures taken (i.e., action taken regarding investigational product in direct relationship to the AE)
6. Seriousness criteria (ie, death, life-threatening, or other criterion)
7. Cause of death
8. Autopsy findings (if available)
9. Name, address, fax number, email, and telephone number of the reporting Investigator (for paper SAER Forms)

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical trial or trials
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor.
In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committees (ECs) and relevant competent authority(s) are notified of the urgent measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (i.e., from the time of signed informed consent up to but not including the first IP exposure) will be described on the SAER. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE.** NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g. reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (e.g., potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) 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. The subject's medical history will also include documented history of on-demand treatment for the past 12 months and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 months.

All medications taken and non-drug therapies received in the 2 weeks prior to study entry and all concomitant medications and non-drug therapies during study will be recorded on the CRFs.

Data on medical history, drug and non-drug therapy history of those subjects who transition from surgery rVWF study will be used from the eCRF of the main studies, will be updated, if applicable, and transcribed into the respective eCRF of the prophy study.

12.6 Physical Examinations

At screening and subsequent study visits (as described in Section 10.3), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 12.1.1.5), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.6.1 Thromboembolic events

Thromboembolic events are considered a potential risk of rVWF treatment, hence, clinical evidence of thrombosis will be monitored during the study. In the case of clinical signs of any thromboembolic event other than superficial thrombosis, additional diagnostic procedures are required according to each institution's standard of care which may consist of, but are not limited to the following:

- For deep vein thrombosis (DVT): Magnetic Resonance Imaging (MRI), compression ultrasound or impedance plethysmography.
- For pulmonary embolism: ECG, chest radiography, perfusion/scintiscan or MRI.
- For myocardial infarction: ECG, cardiac enzymes, echocardiography
- For stroke: diffusion-weighted magnetic resonance imaging or computed tomography, ABCD scoring, carotid imaging

Results of diagnostic procedures may be forwarded to the sponsor to be reviewed by an independent external expert panel, such as the DMC, if applicable.

12.6.2 Anaphylaxis

The diagnosis of anaphylaxis is highly likely when any of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g, generalized urticaria, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:
   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin or mucosal tissue (e.g., generalized urticaria, pruritus or flushing, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to a known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP

If a subject develops anaphylaxis in the course of the clinical study this needs to be reported as SAE (Section 12.1.1.1). Additional blood draws for Anti-VWF IgE antibody testing will be drawn (Section 12.9.13).

12.7 Vital Signs

Vital signs will be assessed pre and post-infusion at each visit, if not stated otherwise:

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

Vital signs (pulse rate, respiratory rate, and blood pressure) should be recorded within 30 min before and after IP administration. The assessment of vital signs per planned study visit is outlined in Supplement 20.2.

Vital sign values are to be recorded on the physical examination eCRF. For each vital sign value, the investigator will determine whether the value is considered an AE (see definition in Section 12.1). If assessed as an AE, the medical diagnosis (preferably), symptom, or sign, will be recorded on the AE eCRF. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE, should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.8 Electrocardiogram

A standard 12-lead ECG at rest will be performed at screening, at the 6 month follow-up visit and at the study termination visit and evaluated for medical significance by the investigator.

12.9 Clinical Laboratory Parameters

Refer to the Laboratory Manual for information on collection and processing of samples.

In general all laboratory tests will be performed at central laboratories, except the pregnancy and blood group test which will be performed at the local laboratory. In addition, relevant critical safety laboratory tests for complete blood count (CBC), serum chemistry and/or coagulation parameters such as VWF and FVIII activity may also be performed in the local laboratory to ensure that results will be available immediately to the investigator. In principle, results from the central laboratory will be used for data analysis purposes. The assays performed in the central laboratories are specified in the Laboratory Manual. The investigator will supply the sponsor with a list of the normal ranges and units of measurement for the laboratory variables to be determined at the site. Laboratory values such as antibodies to other proteins are not required immediately and will be assessed later during the course of the study.

Abnormal laboratory values deemed clinically significant by the investigator are to be recorded as AEs (see Section 12.1.2).

12.9.1 rVWF and endogenous FVIII Pharmacokinetics

PK assessments using a dose of 50 IU ± 5 IU/kg rVWF:RCo will be performed at the baseline visit. If the subject is on on-demand treatment and has received VWF replacement therapy a washout period of at least 5 days is required before the infusion of rVWF for PK assessment can be administered.

Blood samples will be drawn within 30 minutes pre-infusion, and at 7 time points post-infusion (30 ± 5 minutes, 60 ± 5 minutes, 6 ± 1 hours, 12 ± 1 hours, 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours) VWF activity will be determined using the VWF:RCo, VWF:CB and the VWF: Ag assay. The Innovance assay will be used as an exploratory assay to provide supportive data and to compare the results of this new assay with results from the established VWF:RCo assay.

Endogenous FVIII activity will be measured using the 1-stage clotting assay.

At the 12 month ± 2 week visit, a full PK analysis will also be performed. Blood samples will be drawn within 30 minutes pre-infusion, and at 7 time points post-infusion (30 ± 5 minutes, 60 ± 5 minutes, 6 ± 1 hours, 12 ± 1 hours, 24 ± 2 hours, 48 ± 2 hours, 72 ± 2 hours). If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.7.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment.

The following parameters will be used as part of the PK assessment:

- Incremental recovery of VWF:RCo, VWF:Ag, VWF:CB and INNOVANCE VWF Ac (exploratory assay)
- AUC/dose, area under moment curve (AUMC/dose, clearance (CL), Volume of distribution at steady state (V_{ss}), mean residence time (MRT), of VWF:RCo ,VWF:Ag, VWF:CB and INNOVANCE VWF Ac (exploratory assay)
- Half-life of VWF:RCo, VWF:Ag, VWF:CB and INNOVANCE VWF Ac (exploratory assay)
- Time course of the FVIII:C levels
- VWF collagen binding (VWF:CB) levels

12.9.2 Hematology and Clinical Chemistry

The hematology panel will consist of CBC [hemoglobin, hematocrit, erythrocytes (ie, red blood cell count [RBC]), and leukocytes (i.e., white blood cell count [WBC])] with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.

The clinical chemistry panel will consist of sodium (Na), potassium (K), chloride (Cl), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), bilirubin (BILI), alkaline phosphatase (AP), blood urea nitrogen (BUN), creatinine (CR), and glucose (Glu).

Blood will be obtained for assessment of hematology and clinical chemistry parameters at screening, during PK-assessment prior to rVWF IP infusion, after 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours post rVWF IP infusion, at all follow-up visits as per schedule (refer to Supplement 20.3 Clinical Laboratory Assessments), i.e., 4 weeks ± 1week, 8 weeks ± 1 week and every 3 months ± 2 weeks, and at study completion. Hematology and clinical chemistry assessments will be performed on Ethylenediaminetetraacetic acid (EDTA)-anticoagulated whole blood and serum, respectively, at the central laboratory.

12.9.3 Immunology

12.9.3.1 Antibodies to VWF and FVIII

All subjects will be tested for binding and neutralizing antibodies to VWF and FVIII at screening, at baseline PK assessment, at each of the scheduled follow-up visits and at the study completion visit. Testing will be done prior to IP infusion and with at least a 72 hour wash out period since the last IP infusion. If there is any suspicion of inhibitor development (e.g. excessive bleeding) binding and neutralizing antibodies to VWF and FVIII may be tested at the discretion of the investigator.

12.9.3.2 Neutralizing and Total Binding Anti-VWF Antibodies

The assays to establish the presence of neutralizing and total binding anti-VWF antibodies have been established in the absence of international standards and with only limited numbers of positive controls. Therefore, caution is advised in interpreting positive results. In particular, any clinical association, changes in the natural history of the disease, effect of therapy, etc. needs to be taken into account for final judgment. The sponsor's Medical Director should be consulted for additional advice. As part of the AE follow-up, any sample testing positive needs to be confirmed after 2-4 weeks for central laboratory testing. Only confirmed neutralizing anti -VWF antibodies are considered inhibitors (see Section 12.9.3.4). These subjects need to be closely monitored and therapy adjusted accordingly.

12.9.3.3 Binding antibodies to VWF

The presence of total binding anti-VWF antibodies will be determined by an enzyme-linked immunosorbent assay (ELISA) employing polyclonal anti-human Immunoglobulin (Ig) antibodies (IgG, IgM and IgA). For this assay (ELISA), recombinant human VWF will be coated onto a microtiter plate, then incubated with dilutions of the positive control, the negative control or test sample. Antibodies against human VWF that are present in the samples bind to the coated antigen and will be detected with a horseradish peroxidase (HRP)-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a human monoclonal antibody specific for human VWF spiked into the negative control. The negative control for this assay is pooled normal human plasma.

Plasma samples are analyzed for binding antibodies against the specific antigen in two steps. First, the sample is screened for antibodies and the titer of binding antibodies is determined. Second, the specificity of positive antibody results is confirmed.[16]
In brief, all samples are serially diluted (initial dilution 1:20 and further diluted 1:2).

The titer endpoint, defined as the highest dilution that still gives a positive signal above cut off level, is determined in two independent duplicates. The cut off level is established based on background signal level of healthy plasma donors (n=160) and set to include 5% false positives to be as sensitive as possible (95% percentile). The ELISA assay is validated allowing an assay variability of ± 1 titer step. Therefore, differences ≤ 2 titers steps may be due to variability of the ELISA assay. Specificity has to be confirmed in a competition assay when a sample has a titer of 1:80 or higher in the screening assay. Based on the validation criteria samples tested in the screening assay at 1:20 or 1:40 cannot be confirmed in the competition assay. A positive screening value is confirmed if the difference between the titers determined for the subject sample (re-screen) and for the subject sample with pre-incubation (confirmation sample) is > 2 titer steps. Antibody titers of subject samples will only be reported as positive, if the results of the screening and confirmatory analysis fulfill these acceptance criteria. The titer to be reported is always the one determined in the original screening procedure (independent of the result of the re-screening in the confirmation procedure).

A more detailed test procedure will be supplied upon request or pro-actively if a sample tests positive. A treatment related increase of the binding anti-VWF antibodies is expected, if the titer increases by more than 2 titration steps. These subjects need to be closely monitored and therapy adjusted accordingly.

12.9.3.4 Neutralizing antibodies to VWF

Three functional VWF assays, collagen binding (VWF:CB) assay, Ristocetin cofactor (VWF:RCo) and FVIII binding (VWF:FVIIIB), will be used to test for the presence of neutralizing anti-VWF antibodies. Neutralizing antibodies to VWF:RCo, VWF:CB and VWF:FVIIIB activities will be measured by assays based on the Bethesda assay established for quantitative analysis of FVIII inhibitors (Nijmegen modification of the Bethesda assay).[17] The amount of inhibitor is expressed as Bethesda units (BU) per mL. One BU is thereby defined as the amount of inhibitor that decreases the measured activity in the assays to 50% of that of the negative control samples. The assays were validated using human plasma samples from two type 3 VWD patients with low (1-2 BU/mL) and high (~10 BU/mL) titer inhibitors and plasma samples from non-human primates immunized with human rVWF (>100 BU/mL)

If a subject has a measurable baseline level of VWF activity in the respective assay, it is taken into account in the calculation of the residual activity. However, if baseline levels are too high (>15% VWF:RCo), inhibitors may not be reliably detected.

To exclude false positive results, the detection limit for anti-VWF inhibitors was set to 1 BU/ml for all 3 assays. The rationale for this cut-off value is the relatively high CI of the underlying assays, making determinations at the end of the evaluation range of the Bethesda reference curve uncertain.[18]

A more detailed test procedure may be requested to further characterize the anti-VWF inhibitors, if detected.

12.9.3.5 Binding Antibodies to FVIII

Binding antibodies against FVIII will be analyzed using a proprietary enzyme immunoassay. The testing strategy will be as described for binding anti-VWF antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.3.6 Neutralizing antibodies (inhibitors) to FVIII

Neutralizing antibodies (inhibitors) to FVIII will be assessed by the Nijmegen modification of the Bethesda assay in a central laboratory. To verify a FVIII inhibitor, additional testing (such as tests for Lupus anticoagulants) may be initiated. Positive FVIII inhibitor tests will be defined as ≥ 0.4 BU by the Nijmegen-modified Bethesda assay that is confirmed by a second test performed on an independent sample obtained 2-4 weeks following the first test. Only confirmed positive FVIII inhibitor test result will be reported as an SAE.

12.9.4 Antibodies to Other Proteins

Plasma will be assayed for the presence of antibodies against CHO protein (total Ig), murine IgG and human Furin (total Ig) using proprietary enzyme immunoassays. The testing strategy will be as described for binding anti- VWF antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.4.1 Anti-CHO Protein

Total Ig antibodies (IgG, IgA, IgM) against CHO protein will be analyzed. For this assay (ELISA), CHO protein derived from cultures of untransfected cells and propagated under the identical cell culture conditions used for ADVATE production will be coated onto a microtiter plate, then incubated with dilutions of the positive control, negative control or test sample. Antibodies against CHO protein that are present in the samples bind to the coated antigen and will be detected with a horseradish peroxidase (HRP)-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a polyclonal goat anti-CHO protein antibody spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.4.2 Anti-Murine IgG

A commercially available ELISA (Medac, Hamburg, Germany) will be used to detect and to quantify IgG antibodies originating from human plasma that are directed against mouse-IgG (HAMA: human anti- mouse antibodies). Microtiter plates coated with mouse IgG will be incubated with dilutions of the standard, the positive control, the negative control or the test sample. Antibodies against mouse IgG that are present in the samples bind to the coated antigen and form a bridge to a peroxidase coupled mouse IgG antibody that will be used for detection (bridging format of the ELISA assay). The positive control for this assay will be a polyclonal goat anti-murine IgG spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.4.3 Antibodies to human Furin

Total Ig antibodies (IgG, IgA, IgM) against human Furin will be analyzed. For this assay (ELISA), recombinant human Furin will be coated onto a microtiter plate, then incubated with dilutions of the positive control, the negative control or test sample. Antibodies against human Furin that are present in the samples bind to the coated antigen and will be detected with a horseradish peroxidase (HRP)-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a human monoclonal antibody specific for human Furin spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.5 Viral Serology

The following viral seromarkers will be assessed at screening:

- HIV: anti-HIV 1, HIV 2
- HAV: anti-HAV (IgG and immunoglobulin M [IgM])
- HBV: Hepatitis B surface antigen (HbsAg), anti-Hepatitis B (HB) core, anti-HBs
- HCV: anti-HCV ELISA
- Parvovirus B19: anti-B19V (IgG and IgM)

Virus serology will be established during the screening period. The relevant confirmatory Polymerase Chain Reaction (PCR) testing may be performed from appropriate left-over samples as needed.

12.9.6 Urinalysis (Dipstick)

The urinalysis will include assessments for erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite and pH and will be performed at the central laboratory.

12.9.7 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. The pregnancy test may need to be repeated during the course of study in countries where mandated by national law.

12.9.8 VWD Mutational Analysis, Multimer Analysis and Human Leukocyte Antigen Genotyping

A cell pellet (buffy coat and erythrocytes) will be retained at the screening visit for VWD gene mutational analysis, VWF multimer analysis and HLA genotype determination if the information is not already available in the subject's medical history. Results from multimer analysis (see Section 12.9.10.1) may contribute to VWD gene mutational analysis. The genetic testing will be done, when the subject consents to the genetic testing.

12.9.9 Blood Group Analysis

The blood group needs to be determined during the screening period. If the information is not already available in the subject's medical history, it has to be determined at the local lab.

12.9.10 Additional Laboratory Testing in case of Thromboembolic Events

rVWF contains ultra large molecular weight (ULMW) multimers because of a lack of exposure to endogenous VWF protease (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) during the manufacturing process. In vitro and in vivo cleavage of these ultralarge molecular fractions by ADAMTS13 and generation of characteristic satellite bands has been extensively demonstrated during nonclinical and clinical development. Nevertheless, the potential elevated risk of thrombosis and/or other thromboembolic complications due to the administration of ultra large molecular VWF multimers in subjects with normal levels of VWF cannot be completely excluded. Therefore VWF multimer analysis will not only be performed routinely at screening but in case of thromboembolic events both VWF multimer analysis as well as ADAMTS13 activity will be determined to assess any relatedness of these occurrences with IP treatment.

12.9.10.1 VWF multimer analysis

The VWF multimer pattern will be assessed using low-resolution sodium dodecyl sulfate (SDS)–agarose gel electrophoresis. High-resolution SDS–agarose gel electrophoresis, with agarose concentrations >1.5%, will be used to determine the satellite band structure of VWF. These analyses will employ Western blot with luminescence video imaging.

12.9.10.2 ADAMTS13 activity

VWF73 was identified as the 73 amino acid minimal region of the VWF A2 domain required for ADAMTS13 cleavage. The cleavage of this substrate will be detected by a commercially available ELISA-based Chromogenic assay (Technoclone Austria): Cleavage of immobilized VWF73 substrate is detected by a HRP-labeled antibody directed against the cleavage site of VWF73. The amount of bound antibody, which is the function of the ADAMTS13 cleavage is detected by a chromogenic substrate.

12.9.11 Soluble P-Selectin (sP-Selectin)

sP-selectin is a cell adhesion molecule (CAM) found in granules in endothelial cells (cells lining blood vessels) and activated platelets. Data for an association between the sP-selectin concentration, thrombotic thrombocytopenic purpura (TTP) and venous thromboembolism (VTE) are limited and the predictive value has not yet established. A commercial ELISA assay will be employed as an exploratory test. sP-selectin will be determined at the Screening visit and used as indicator for an increased thrombotic risk.

12.9.12 D-Dimer

D-dimer will be used as a marker for DVT and disseminated intravascular coagulation (DIC). While a negative result practically rules out thrombosis, a positive result can indicate thrombosis but does not rule out other potential etiologies, including a recent hemorrhage. Its main use, therefore, is to exclude thromboembolic disease where the probability is low. D-Dimer will be measured at the Screening visit and used as indicator for an increased thrombotic risk.

12.9.13 Additional Laboratory Testing in Case of Severe Hypersensitivity Reactions

If a subject develops a severe hypersensitivity reaction in the course of the clinical study, additional blood draws for anti-VWF IgE antibody testing will be drawn. The presence of anti-VWF IgE will be determined by using the ImmunoCAP®, a VWF-specific IgE blood test (Thermo Scientific). The basis of the ImmunoCAP® technology is a cellulose polymer as solid phase in a plastic capsule providing a large surface for protein binding. rVWF as antigen is covalently coupled to the cellulose polymer. Detection of specific anti-VWF IgE bound to the antigen will be accomplished by a secondary enzyme-labeled

anti-human IgE antibody. Testing for binding anti-human VWF IgE antibodies will be done with 0.5 mL plasma. Antibody containing samples will be identified and quantified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.14 Exploratory Assay

The INNOVANCE VWF Ac: an assay, which will eventually replace the VWF:RCo test in the future, will be done using the same time points/blood draws including PK assessment as outlined for the VWF:RCo assessments. The VWF Ac assay is a sensitive test for direct determination of VWF activity. It employs an advanced new technology, allowing the assay to mimic the reaction in which VWF binds to glycoprotein Ib (GPIb), the major VWF receptor protein on platelets. Latex particles are coated with an antibody against GPIb, to which recombinant GPIb is added.

12.9.15 Assessment of Laboratory Values

12.9.15.1 Assessment of Abnormal Laboratory Values

For VWF and FVIII laboratory assessments no evaluation of clinical significance is necessary.

Each other laboratory value (except results to determine genetics of the underlying VWD disease and blood group) has to be assessed by the investigator and the assessment will be recorded on the eCRF. The investigator will determine for each abnormal laboratory value whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 12.1) and record the sign, symptom, or medical diagnosis on the AE CRF, is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.5), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, i.e. because it is due to a preexisting disease, due to a lab error, due to variation or due to another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

Any seroconversion result for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V) shall be re-tested.

12.10 [redacted]

12.10.1 [redacted]

[redacted]

12.10.2 [redacted]

[redacted]

13. STATISTICS

13.1 Sample Size and Power Calculations

The determination of the sample size for this study is not based on strict statistical considerations. The sample size of a subset of at least 15 subjects with severe VWD, 5 of whom must have Type 3 VWD, is based on the Guideline on the Clinical Investigation of Human Plasma Derived von Willebrand Factor Products (CPMP/BPWG/220/02).[1]

13.2 Datasets and Analysis Cohorts

13.2.1 Safety Analysis Set

The Safety Analysis Set will be composed of all subjects who received any amount of IP, rVWF:ADVATE or rVWF alone.

13.2.2 Full Analysis Dataset

The Full Analysis Set (FAS) will be composed of all subjects with available bleeding data gathered during prophylaxis IP treatment.

13.2.3 Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set will be composed of subjects who are at least 70% compliant regarding required prophylactic infusions. Only subjects who met all study entry criteria and who had no major protocol violations that might impact efficacy assessments will be included in the PP analysis set.

13.2.4 PK Full Analysis Set

The Pharmacokinetic Full Analysis Set (PKFAS) will be composed of all subjects who received the PK infusion and who provided acceptable data for PK analysis. Acceptable PK data will be defined in the Statistical Analysis Plan.

13.2.5 PK Per Protocol Analysis Set

The Pharmacokinetic 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 affecting the PK period of the study as defined in the detailed Statistical Analysis Plan.

13.3 Handling of Missing, Unused, and Spurious Data

13.3.1 General

Statistical techniques will not be used to identify and exclude any observations as outliers from the analyses. If data are considered spurious, e.g. for lack of biological plausibility, it will be documented to include the reason for exclusion and the analyses from which the data were excluded.

13.3.2 Other

1. Regarding missing data in PK records:
   - Body weight: If a subject's weight is missing from the PK infusion record, the subject's last recorded weight will be used to calculate the weight-adjusted dose.
   - Concentration:
   - Baseline concentration levels reported as below the limit of quantification will be considered to be 0. Missing VWF baseline concentration levels (VWF: RCo, VWF: AG or VWF: CB) for Type 3 subjects will be set to 0.
   - Time:
   - If start time of infusion is missing (but stop time is available) and actual collection time is available, then stop time of infusion will be taken for further calculation (i.e. time difference between actual end date/time of infusion and date/time blood sample drawn).
     - If actual collection date/time is missing and planned collection date/time is missing, then this PK time point will be taken out from the PK analysis (i.e. no data entry for this time point).
     - For all other scenarios, the planned collection date/time will be taken for further calculation.
2. Regarding missing data in AE records:
   - Handling of unknown causality assessment:
     - If a subject experiences an AE with a missing causality assessment, the relationship of the AE will be counted as "related."
   - Handling of unknown severity grades:
     - If a subject experiences more than one AE categorized under the same preferred term, 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.

13.4 Methods of Analysis

The study success criteria are the objectives as stated in Section 7. “Treatment success” was defined as the extent of control of bleeding episodes achieved during this study.

13.4.1 Primary Outcome Measure

The statistical analysis will provide descriptive summaries.

For the number of infusions and for the total weight adjusted consumption of rVWF and ADVATE per month and per year during on-demand treatment, summary statistics will be carried out.

For the number (proportion) of subjects with reduction of ABR relative to historic ABR as well as for the number (proportion) of subjects with 0 bleeds, proportions and corresponding 95% two-sided CIs will be performed.

The annualized rate of bleeding episodes will be calculated as (Number of bleeding episodes/observed treatment period in days) * 365.25.

The primary efficacy analysis will be based on the FAS. As a supportive analysis, the same analysis will also be carried out on the PP.

The two time periods (prior to prophylaxis treatment and while on prophylaxis) will be compared within each subject in terms of mean ABR using a generalized estimating equations model framework (with a logarithmic link function which was the default for the negative binomial distribution), accounting for the fixed effect of the two time periods. The follow-up time (in years) will be specified as an offset and an unstructured working correlation matrix will be used to account for the correlated data. Ratios between the two time period means (95% CI) will be estimated within this model by SAS procedure GENMOD.

13.4.2 Secondary Outcome Measures

13.4.2.1 Efficacy

For the number of infusions and for the total weight adjusted consumption of rVWF and ADVATE per month and per year during on-demand treatment for bleeding episodes, summary statistics will be carried out.

For the number (proportion) of subjects with reduction of ABR relative to historic ABR as well as for the number (proportion) of subjects with 0 bleeds, proportions and corresponding 95% two-sided CIs will be performed.

The cause, type, localization and severity of bleeding episodes will also be recorded and summarized. Bleeding episodes should be organized by where they occur in addition to whether they occurred spontaneously or due to a traumatic event.

The secondary efficacy analysis will be performed on the FAS only.

13.4.2.2 Efficacy of the Treatment of Bleeding Episodes

For the number of infusions of rVWF and ADVATE per bleeding episode, for the weight adjusted consumption of rVWF and ADVATE per bleeding event as well as for the overall hemostatic efficacy rating at resolution of bleed, summary statistics will be carried out.

The severity and localization of bleeding episodes will also be recorded and summarized.

The analysis will be performed on the FAS.

13.4.2.3 Pharmacokinetic Analysis

All PK analyses will use the actual sampling times, not nominal times specified in the protocol, wherever possible. Actual sampling times will be defined as time from the start of infusion to the blood sample collection time. A deviation from the protocol-specified blood sample 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 results were biologically implausible will be eliminated from the analysis.

If any concentration data are considered spurious (e.g. lack of biological plausibility), the reason for exclusion from the analysis and the analysis from which the data point was excluded will be documented.

To ensure that values at baseline (pre-infusion) are not affecting the estimation of PK parameters, post-infusion concentration data will be adjusted for baseline as follows:

$$C_{Corrected,\ t} = (1 - \frac{C_{Measured,\ pre-infusion}}{C_{Measured,\ Tmax}}) \cdot C_{Measured,\ t}$$

After adjustment of the post-infusion concentration data, any pre-infusion data will be set to 0.

$C_{Corrected}$ will be set to missing, if:

- Samples have an unknown draw time or where the concentration could not be determined, or where results were deemed to be unreliable due to analytical issues.
- Any concentration data are considered spurious (e.g. lack of biological plausibility).

Handling of concentrations that are below the quantification limit:

- Baseline concentration values reported as below the limit of quantification will be considered to be 0 ($\rightarrow C_{Corrected}$ = Concentration value)
- Post-infusion concentration values reported as below the limit of quantification or missing repeated concentration values will be set to missing ($\rightarrow C_{Corrected}$ = missing)

The area under the plasma concentration/time curve from time 0 to infinity ($AUC_{0-\infty}$) and the area under the first moment curve from time 0 to infinity ($AUMC_{0-\infty}$) will be calculated as the sum of AUC or AUMC from time 0 to the time of last quantifiable concentration plus a tail area correction calculated as C_t/λ_z and $C_t/\lambda_z(t + 1/\lambda_z)$, respectively, where C_t is the last quantifiable concentration, t is the time of last quantifiable concentration and λ_z is the terminal or disposition rate constant.

The area under the plasma concentration/time curve from time 0 to 72 hours post-infusion (AUC_{0-72h}) will be computed using the linear trapezoidal rule. For the calculation of AUC_{0-72h} the levels at 72 hours will be linearly interpolated/ extrapolated from the 2 nearest sampling time points.

Elimination phase half-life (HL) in hours will be calculated as:

$$T_{1/2} = log_e(2)/\lambda_z$$

where the elimination rate constant (λ_z) will be obtained by $\log_e$-linear fitting using least squares deviations to at least the last 3 quantifiable concentrations above pre-infusion level.

The **Mean Residence Time** (MRT) in hours will be calculated as total area under the moment curve divided by the total area under the curve:

$$MRT = \frac{AUMC_{0-\infty}[h^2 * IU/dL]}{AUC_{0-\infty}[h * IU/dL]}$$

Systemic clearance in dL/kg/h will be calculated as the dose in IU/kg divided by the total AUC:

$$CL = \frac{Dose[IU/kg]}{AUC_{0-\infty}[h * IU/dL]}$$

Apparent **steady state volume of distribution** (Vss) in dL/kg will be calculated as:

$$Vss = \frac{Dose[IU/kg] \times AUMC_{0-\infty}[h^2 * IU/dL]}{AUC^2_{0-\infty}[h^2 * IU^2/dL^2]}$$

The **maximum concentration**, C_{max}, will be calculated as the maximum concentration post-infusion.

The **time to reach the maximum concentration**, T_{max}, in hours was defined as the time to reach C_{max}.

Incremental recovery (IR) in (IU/dL)/(IU VWF:RCo/kg) will be calculated as:

$$IR = \frac{C_{max}[IU/dL] - C_{pre-infusion}[IU/dL]}{dose\ per\ kg\ body\ weight\ [IU/kg]}$$

where C_{max} and $C_{pre\text{-}infusion}$ are the unadjusted concentration values.

The PK parameters $AUC_{0\text{-}72h}$/Dose, $AUC_{0\text{-}\infty}$/Dose, $AUMC_{0\text{-}\infty}$/Dose, MRT (mean residence time), CL (clearance), IR (incremental recovery), $T_{1/2}$ (elimination phase half-life), Vss (Volume of distribution at steady state), C_{max} (maximum concentration) and T_{max} (time to reach the maximum concentration) will be summarized by mean, standard deviation and the corresponding 90% CIs, median, Q1, Q3, IQR and range.

Descriptive statistics will be used to summarize VWF:RCo levels for each nominal time point on the PK curve.

PK analysis as described above will be carried out on the PKFAS as well as on the PKPPAS.

For all subjects in the PKFAS concentration vs. time curves will be prepared.

PK parameters will be derived using non-compartmental methods in WinNonlin.

The analysis will be performed on the FAS.

13.4.2.4 Safety

AEs that occurred during or within 24 hours after first IP infusion will be presented in summary tables. Summary tables shall indicate the number of subjects who experienced adverse events. Separate tables will be carried out for temporally associated adverse events; and for temporally associated or causally related adverse events.

In addition, tables will be prepared to list each AE, the number of subjects who experienced an AE at least once, and the rate of subjects with AE(s). AEs will be grouped by system organ class. Each event will then be divided into defined severity grades (mild, moderate, severe). The tables will also divide the AEs into those considered related (a "possibly related" or a "probably related" AE will be considered as a "related AE") to the treatment and those considered unrelated (an "unlikely related" or a "not related" AE will be considered as an "unrelated" AE). These tables will also be carried out for temporally associated adverse events; and for temporally associated or causally related adverse events.

All AEs; temporally associated AEs; causally related AEs (by investigator assessment); and temporally associated or causally related AEs will also be summarized by system organ class, preferred term, including the number of AEs, the number (%) of unique subjects, the frequency category (very common: ≥10%, common: ≥1% to <10%, uncommon: ≥0.1% to <1%, rare: ≥0.01% to <0.1%, very rare: <0.01%) and the number of IP-infusions associated with an AE.

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 infusion, irrespective of being related or not related to treatment.

AEs and SAEs for each subject, including the same event on several occasions, will be listed separately, giving both MedDRA preferred term and the original verbatim term used by the investigator, system organ class, severity grade, seriousness, relation to the treatment (by investigator assessment; for SAEs this will be by investigator and sponsor assessment), onset date, and stop date.

AEs that occurred before first IP infusion will be listed separately.

Incidences of thromboembolic events and hypersensitivity reactions will be tabulated and also listed per subject. For the development of antibodies, proportions will be carried out.

The safety analyses will be based on the safety analysis set.

13.5 Exploratory Outcome Measures

13.6 Planned Interim Analysis of the Study

No formal interim analysis is planned for this study. However, a descriptive summary report for this study is planned after all subjects have completed at least 6 months of prophylactic treatment with rVWF.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Trial Agreement (CTA). If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the CTA.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable national and local regulatory requirements as described in the CTA. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

15.1.1 Investigator Report and Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the CTA. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the CTA. Auditing processes specific to the study will be described in the audit plan.

15.5 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor (Baxalta) will also ensure the responsible EC and relevant competent authority are notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.6 Laboratory and Reader Standardization

A central laboratory/reader will be used for all clinical assessments except for pregnancy testing and blood group test (refer to Section 12.9). Local laboratories are requested to provide their laboratory specifications of the individual tests that are also being tested locally.

16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the CTA.

16.2 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the CTA.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

16.3 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients and/or their legally authorized representative must sign an informed consent form before entering into the study according to applicable national and local regulatory requirements and ICH GCP. Before use, the informed consent form will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 16.2). The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable national and local regulatory requirements. Patients or their legally-authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent form, patients or their legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised informed consent form, which have been approved by the applicable EC and regulatory authorities, will be provided by the investigator to the subjects who consented to participate in the study

16.4 Data Monitoring Committee

This study will be monitored by Data Monitoring Committee (DMC). The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. 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 stop a trial if it finds toxicities or if treatment is proven to be not beneficial. Details will be defined in the DMC charter.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the CTA.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.8), records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, CRFs, SAERs, laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

If electronic format CRFs are provided by the sponsor, only authorized study site personnel will record or change data on the CRFs. If data is not entered on the CRFs during the study visit the data will be recorded on paper and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (e.g., ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the CTA.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the CTA.

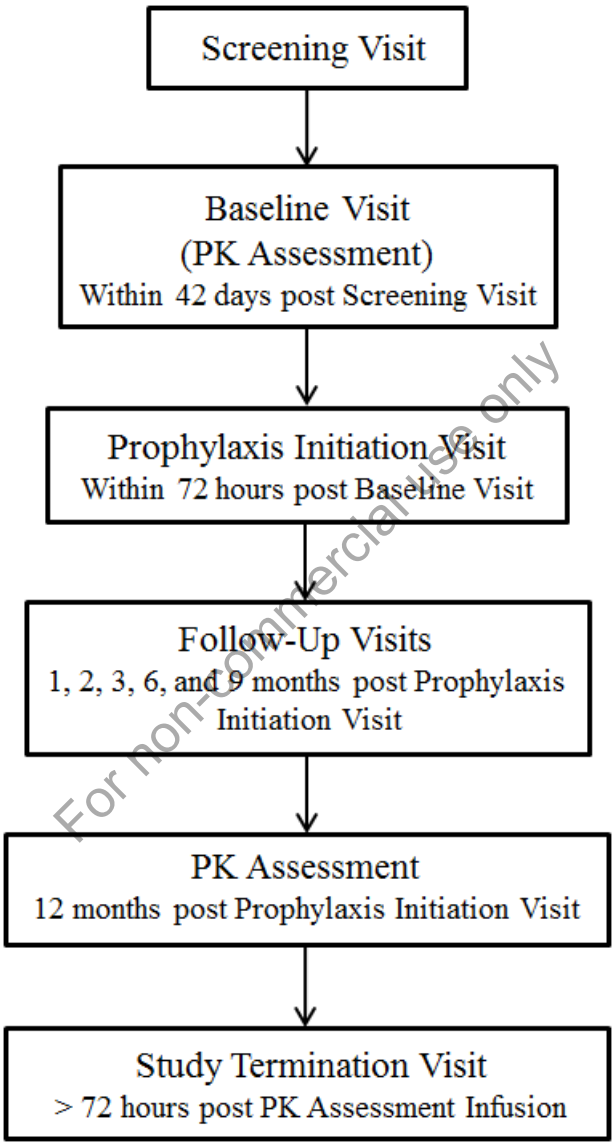
19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the CTA.

20. SUPPLEMENTS

20.1 Study Flow Chart

Figure 1
Study Design for Baxalta Clinical Study 071301



20.2 Schedule of Study Procedures and Assessments

Table 5
Schedule of Study Procedures and Assessments

Procedures/ Assessments	Screening Visit	Baseline Visit (PK-assessment visit)			Prophylaxis Initiation Visit	Interval/Follow-Up Study Visits					PK Assessment and Study Completion			Termination Visit
		Pre-infusion	Infusion	Post-infusion[g]		1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion	Infusion	Post-infusion[g]	Conducted at the 72 hour postinfusion PK Assessment
											12 month± 2 weeks			
Informed Consent [a]	X													
Eligibility Criteria	X													
Medical History[b]	X	X									X			
Medications[c]	X	X			X	X	X	X	X	X	X			X
Non-drug Therapies[c]	X	X			X	X	X	X	X	X	X			X
Physical Exam	X	X			X	X	X	X	X	X	X			X
Adverse Events		X			X	X	X	X	X	X	X			X
Bleeding Episodes	X	X			X	X	X	X	X	X	X			X
Laboratories	X	X		X	X[h]	X	X	X	X	X	X		X	X
Vital Signs[d]	X	X		X	X	X	X	X	X	X	X		X	X
ECG	X								X					X
IP Treatment[e]			X		X	X	X	X	X	X		X		
IP Consumption / Treatment Compliance						X	X	X	X	X				
Subject Diary					X	X	X	X	X	X				
[redacted]	X[f]								X					X

Continued on next page

Continued

[a]) Occurs at enrollment (before screening).
[b]) Including documented history of on-demand treatment for the past 12 months and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 months.
[c]) Including all medications and non- drug therapies taken in the 2 weeks prior to study entry and all the concomitant medications and non-drug therapies during the course of the study.
[d]) Vital signs (pulse rate, respiratory rate, and blood pressure): within 30 minutes before infusion start and 30 ± 15 minutes post-infusion.
[e]) IP treatment after the prophylactic treatment initiation visit at the site will be continued as home-treatment if the subject qualifies; a wash-out period of at least 72 hours is required after the last IP infusion before the follow-up visit. IP infusion will be given at the study site after the blood sample for immunology testing and IR determination is drawn.
[f]) Can be done either at the screening or the baseline visit.
[g]) Time points for blood draws post infusion: 30 ± 5 minutes; 60 ± 5 minutes; 6 ± 1 hours; 12 ± 1 hours; 24 ± 2 hours; 48 ± 2 hours; 72 ± 2 hours.
[h]) If a subject did not undergo PK assessment (for example the subject has participated in the surgery study **071101** and has undergone PK in Study **071101**), laboratory assessments will be performed at this visit.

20.3 Clinical Laboratory Assessments

Table 6
Clinical Laboratory Assessments

Procedures/ Assessments	Screening Visit	Baseline Visit (PK-assessment visit)			Prophylaxis Initiation Visit[k]	Interval/Follow-Up Study Visits					PK Assessment and Study Completion			Termination Visit
		Pre-infusion	Infusion	Post-infusion[g]		1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion	Infusion	Post-infusion[g]	Conducted at the 72 hour postinfusion PK Assessment
											12 month± 2 weeks			
Hematology [a]	X	X		X	X	X	X	X	X	X	X[m]		X	
Clinical Chemistry[b]	X	X		X	X	X	X	X	X	X	X		X	
Coagulation Panel/PK assessment[c]	X	X		X	X	X	X	X	X	X	X		X	
Immunogenicity[d]	X	X		X	X[l]	X	X	X	X	X	X		X	
Viral Serology[e]	X													
Urinalysis[f]	X													
VWD Gene Mutational Analysis / HLA genotype analysis and Analysis of VWF multimers[g]	X													
sP-selectin and D-dimer	X[h]													
Blood Group[i]	X								X					
Pregnancy Test[j]	X													
Exploratory Tests	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Continued

[a] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. Hematology assessments during PK assessments will be determined prior IP infusion and 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours thereafter.

[b] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin. Clinical chemistry will be determined at baseline, after 24 ± 2 h, 48 ± 2 hours and 72 ± 2 hours during the PK assessments.

[c] Coagulation panel/PK assessment: INR/aPTT, VWF:RCo, VWF:Ag, VWF:CB, FVIII:C, VWF Innovance (exploratory assay); during the PK assessment at the baseline visit blood samples will be drawn 30 min prior PK infusion; once the PK infusion is completed 30 ± 5 minutes; 60 ± 5 minutes; 6 hours ± 1 hour ; 12 ± 0.5 hours; 24 ± 2 hours, 48 ± 2 hours; 72 ± 2 hours and VWF:RCo, VWF:CB, VWF:Ag, VWF Ac, FVIII:C will be determined; in case of thromboembolic event VWF multimers and ADAMTS13 will be analyzed to judge on a possibly relatedness to UHMW fractions of the IP.

[d] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII – Neutralizing and Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG; .CD4* In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined. A washout period of at least 72 hours after the last IP infusion is required before blood samples for immunogenicity assessments can be drawn.

[e] Viral Serology 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; HIV-1/HIV-2 Antibodies

[f] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH

[g] Not required if available in the subject's medical history; VWF multimers: additionally in case of thromboembolic events

[h] At screening and in case of thromboembolic events

[i] Blood group assessment major blood group (local laboratory) only if not available in the subject's medical history

[j] Serum pregnancy test (in females of child-bearing potential if no urine sample is available)

[k] The 72 h post-infusion laboratory assessments coincidence with the initiation visit for prophylactic treatment. After the blood samples are drawn for laboratory assessment for the 72 h post infusion PK assessment, the subject receives the first IP infusion for prophylactic treatment (prophylactic treatment initiation visit).

[l] Only needed for subjects without PK assessment prior to their first IP infusion in this study.

[m] A full PK analysis will be performed. Blood samples will be drawn within 30 minutes pre-infusion, and at 7 time points post-infusion (30 ± 5 minutes, 60 ± 5 minutes, 6 ± 1 hours, 12 ± 1 hours, 24 ± 2 hours, 48 ± 2 hours, 72 ± 2 hours).

21. REFERENCES

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22. SUMMARY OF CHANGES

Protocol 071301: Amendment 1: 2016 APR 08

Replaces: Original: 2014 FEB 19

In this section, changes from the previous version of the Protocol, dated 2014 FEB 19, are described and their rationale is given.

1. Throughout the document
   Description of Change: Minor edits and formatting corrections. The sponsor name was updated from 'Baxter' to 'Baxalta' and the dates of the planned study period were updated. The term 'inhibitory antibodies' was updated to 'neutralizing antibodies' and 'thrombotic' was updated to 'thromboembolic', throughout the protocol. The abbreviation [redacted] was corrected to [redacted] throughout the protocol. The term 'allergic' was changed to 'hypersensitivity' for consistency across program documents. Some updates were made as a result of a newly available protocol template. EudraCT number added.
   Purpose for Change: Administrative.

2. Synopsis, Primary Objective; Synopsis, Primary Outcome Measure; Section 7.2 Primary Objective; Section 8.4.1 Primary Outcome Measure; Section 13.4.1 Primary Outcome Measure
   Description of Change: The description of ABR for the primary objective was updated. It was clarified that spontaneous bleeding episodes were those not related to trauma.
   Purpose for Change: Administrative.

3. Synopsis, Secondary Objectives; Section 7.3 Secondary Objectives
   Description of Change: Immunogenicity was added to the list of secondary objectives for consistency with the listed secondary outcome measures.
   Purpose for Change: Administrative.

4. Synopsis, Exploratory Objectives; Synopsis, Exploratory Outcome Measures; Section 7.4 Exploratory Objectives; Section 8.4.3 Exploratory Outcomes Measures; Section 13.5 Exploratory Outcomes Measures
   Description of Change: [redacted] were added as an exploratory objective and exploratory outcome measures.
   Purpose for Change: Administrative.

5. Synopsis, Study Design; Section 8.3 Duration of Study Periods and Subject Participation
   Description of Change: The planned duration of the participation period for subjects was updated from 16 months to 15 months.
   Purpose for Change: Administrative.

6. Synopsis, Study Design; Section 8.3 Duration of Study Periods and Subject Participation
   Description of Change: Language was included regarding an option for subjects to enrol into a continuation study once all visits in 071301 have been completed: "Subjects will be offered the option to continue to receive BAX111 in a long-term continuation study".
   Purpose for Change: It would be unethical to remove access to the study drug while it remains unapproved for commercial, prophylactic use, hence a long-term continuation study will allow continued access to BAX111 and additionally allow longer term data to be collected.

7. Synopsis, Secondary Outcome Measures; Synopsis, Planned Statistical Analysis, Section 8.4.2.1 Efficacy, Section 8.4.8.4 Efficacy of the Treatment of Bleeding Episodes; Section 13.4.2.1 Efficacy
   Description of Change: To clarify that the secondary outcome measure of "Number of infusions and total weight adjusted consumption of rVWF and ADVATE (recombinant factor VIII/rFVIII) per month and per year" referred to on-demand treatment and not prophylactic treatment. It was also clarified that spontaneous bleeding episodes were those that were unrelated to trauma. The number of infusions and weight-adjusted consumption of rVWF and ADVATE per traumatic bleeding episode were added as secondary outcome measures for the efficacy of the treatment of bleeding episodes.
   Purpose for Change: Clarification of secondary outcome measure due to FDA feedback.

8. Synopsis, Active Product; Section 8.2 Overall Study Design;
   Section 8.7.4.3 Prophylaxis Treatment
   Description of Change: The dosage frequency was changed and clarified for those subjects transitioning from on-demand treatment on entry to the study.
   A new subsection (Section 8.7.4.3.1) was added to describe the criteria for treatment escalations.
   Purpose for Change: Administrative.

9. Synopsis, Targeted Accrual
   Description of Change: The text was updated to clarify that approximately 18 subjects would be enrolled to achieve 15 evaluable subjects with severe VWD.
   Purpose for Change: Administrative.

10. Synopsis, Inclusion Criteria; Section 9.1 Inclusion Criteria
    Description of Change: The definition of severe VWD was added to the protocol. Inclusion criteria regarding diagnosis of VWD and prior treatment were clarified. Clarification was added regarding past documented spontaneous bleeds requiring VWF treatment. An acceptable body mass index range was added to the inclusion criteria.
    Purpose for Change: EMA feedback.

11. Synopsis, Inclusion Criteria; Synopsis, Exclusion Criteria; Section 9.1 Inclusion Criteria; Section 9.2 Exclusion Criteria
    Description of Change: Study entry criteria were amended to exclude subjects receiving prophylaxis prior to entering the study. The study aims to demonstrate a change in ABR from pre-study to prophylaxis with BAX111 and having patients already on prophylaxis would negatively impact this possibility.
    Purpose for Change: Due to the low number of patients involved in the trial, only half of the subjects would be on-demand treatment at the time of enrollment.

12. Synopsis, Exclusion Criteria; Section 9.2 Exclusion Criteria
    Description of Change: An exclusion criterion was added for those who have received prophylaxis treatment in the 12 months prior to screening (including those who received treatment once a month for menorrhagia but were not treated for any other bleeds).
    Purpose for Change: In light of the small number of subjects, the protocol was revised in order to evaluate only subjects currently receiving on-demand therapy.

13. Synopsis, Exclusion Criteria; Section 9.2 Exclusion Criteria
    Description of Change: Subjects with Type 2N VWD are to be excluded from the study. Subjects with cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia) are to be excluded from the study. It was added that subjects with a low platelet count should be excluded from the study. It was also added that subjects receiving prophylaxis treatment at a dosing frequency of once per week would be excluded from the study.
    Purpose for Change: EMA feedback.

14. Synopsis, Sample Size Calculation; Section 13.1 Sample size and Power Calculation, Section 22 References
    Description of Change: The following text was added to clarify the choice of sample size, and the corresponding reference was added to the protocol:
    New text: The sample size of a subset of at least 15 subjects with severe VWD, 5 of whom must have Type 3 VWD, is based on the Guideline on the Clinical Investigation of Human Plasma Derived von Willebrand Factor Products (CPMP/BPWG/220/02).
    Purpose for Change: To justify the sample size chosen for the protocol.

15. Synopsis, Planned Statistical Analysis; Section 11.1 Assessment of Spontaneous Bleeding Episodes/Annualized Bleed Rate; Section 13.4.2.1 Efficacy
    Description of Change: Bleeding episodes should be organized by where they occur in addition to whether they occurred spontaneously or due to a traumatic event.
    Purpose for Change: Bleeding episodes due to traumatic events should not be included in the calculation of ABR.

16. Synopsis, Planned Statistical Analysis; Section 13.4.1 Primary Outcome Measure; Section 13.4.2.1 Efficacy
    Description of Change: The 90% CIs for the primary and secondary outcome measures were updated to 95% CIs. Text was added to Section 13.4.1 to describe the difference between prospective and historical ABR.
    Purpose for Change: EMA request to change.

17. Synopsis, Planned Statistical Analysis; Section 13.4.2.1 Efficacy
    Description of Change: It was clarified that the number of infusions and the total weight adjusted comparison of rVWF and ADVATE (per month/year) will be calculated during on-demand treatment *for bleeding episodes*.
    Purpose for Change: Administrative.

18. Synopsis, Planned Statistical Analysis; Section 13.4.2.1 Efficacy; Section 13.4.2.2 Efficacy of the Treatment of Bleeding Episodes
    Description of Change: It was added that the cause, type, localization and severity of spontaneous bleeds were to be documented throughout the study.
    Purpose for Change: EMA feedback.

19. Section 2 Serious Adverse Event Reporting, Section 12.1.2 Assessment of Adverse Events
    Description of Change: Text added to clarify that bleeding events meeting seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) should be reported on the SAE eCRF or SAE Report form as an SAE.
    Purpose for Change: Compliance with Baxalta SOP for reporting cases that meet CIOMS criteria for seriousness.

20. Section 6.1 Description on Investigational Product
    Description of Change: Text was added to describe the licensure of rVWF in the US.
    Purpose for Change: Administrative.

21. Section 6.3 The role of prophylaxis in the management of VWD; Section 22 References
    Description of Change: Further details of the prospective component of the VIP trial recently became available so a summary of the results were added along with the corresponding reference.
    Purpose for Change: Administrative.

22. Section 6.5 Findings from Nonclinical and Clinical Studies;
    Section 6.5.2 Findings from Clinical Studies; Section 22 References
    Description of Change: Details from the completed phase 3 study 071001 were added to the protocol. Section 6.5.2 was amended to include Study 071001 and the corresponding reference was added to the protocol.
    New sub-sections were added to include a summary of the study design and results for 071001(Section 6.5.2.3) and to add details of expanded access in a single subject with VWD in 071401 (Section 6.5.2.4).
    Purpose for Change: Updated list of completed studies.

23. Section 8.6 Study Stopping Rules
    Description of Change: A new study stopping criterion was added for those subjects with abnormal liver function.
    Purpose for Change: Administrative.

24. Section 8.7.3 Administration
    Description of Change: It was added that the IP infusions should be administered over a duration of 2 to 15 minutes, depending on the volume.
    Purpose for Change: Administrative.

25. Section 8.7.4.1 Baseline Visit (PK-Assessment Treatment);
    Section 8.7.4.2 Prophylaxis Initiation Treatment; Section 10.3.1 Screening Visit;
    Section 20.1 Study Flow Chart
    Description of Change: The duration of the screening period was changed from 60 days to 42 days.
    Purpose for Change: Administrative.

26. Section 8.7.4.1 Baseline Visit (PK-Assessment Treatment);
    Section 8.7.4.2 Prophylaxis Initiation Treatment; Section 10.3.3.1 Surgical Prophylaxis; Section 10.3.2 Baseline Visit – PK-Assessment Visit;
    Section 20.2 Study Flow Chart
    Description of Change: The text regarding subjects transitioning from the surgery study 071101 was updated to reflect the fact that the surgery study will have completed enrollment prior to this study enrolling the first subject. Subjects who participated and had a major procedure performed in the surgery study 071101 will not need an additional PK assessment in this study. Subjects who participated and had a minor procedure performed in the surgery study 071101 will need a PK assessment. Section 10.3.3.1 was removed from the protocol.
    Purpose for Change: The surgery study will complete enrollment prior to this study enrolling the first subject.

27. Section 8.7.4.3 Prophylaxis Treatment; Table 1 rVWF Dosing Schedule Examples: Schedules, A, B, and C; Section 8.7.4.3.1 Treatment escalation; Table 2 Criteria for escalation specific to each bleeding indication
    Description of Change: Schedule C removed.
    Purpose for Change: Since the study no longer offers an every other day dosing frequency, this schedule has been removed.

28. Section 8.7.4.3.1 Treatment escalation; Table 2 Criteria for escalation specific to each bleeding indication
    Description of Change: Text added to instruct investigators how to treat a bleed if it occurs when the subject is receiving BAX111 3 times per week.
    Purpose for Change: Details added since the every other day dosing frequency was removed.

29. Section 8.7.4.4.2 Dosing Recommendations for Treatment of Bleeding Episodes
Description of Change: A definition of menorrhagia was added to the protocol.
Purpose for Change: Administrative.

30. Section 10.3.1 Screening Visit; Section 12.9.8 VWD Mutational Analysis, Multimer Analysis and Human Leukocyte Antigen Genotyping
Description of Change: It was clarified that VWD has to be confirmed by genetic testing and multimer analysis, either by the subjects's medical history or by sample assessment during screening.
Purpose for Change: Clarification of screening assessments.

31. Section 10.3.1 Screening Visit; Section 10.3.5 Follow-Up Visits (1 Month ± 1 Week, 2 Months ± 1 Week, 3 Months ± 2 Weeks, 6 Months ± 2 Weeks, 9 Months ± 2 Weeks); Section 10.5 Subject Diary; Section 11.1 Assessment of Spontaneous Bleeding Episodes/Annualized Bleed Rate
Description of Change: The information to be recorded in the subject diary was updated; potency, lot numbers, weight, AEs, concomitant medication and drug accountability were removed and it was clarified that the treatment of both spontaneous and traumatic bleeding episodes were to be recorded. It was also added that infusions performed at the study site will be recorded in the site's source documents and not in the patient diary. Additional clarification was added on where bleeding episodes will be recorded. It was added that, when possible, site visits should be scheduled on days when the subject is expected to infuse BAX 111.
Purpose for Change: Administrative.

32. Section 10.3.7 Study termination Visit (12 months ± 2 weeks);
Section 12.9.1 rVWF and Endogenous FVIII Pharmacokinetics;
Section 20.2 Schedule of Study Procedures and Assessments;
Section 20.3 Clinical Laboratory Assessments
Description of Change: Full PK analysis was added at the end of the study to allow comparison to the baseline PK parameters.
The full PK assessments and a study termination visit to coincide with the 72-hour postinfusion PK analysis was added to Table 5 and Table 6.
Purpose for Change: To allow comparative analysis of PK parameters at baseline and at the end of the study.

33. Section 10.3.7 Study termination Visit (12 months ± 2 weeks)
    Description of Change: Subjects will be offered the option to continue to receive BAX111 in a long-term continuation study.
    Purpose for Change: Strategic decision to allow access to BAX111 for subjects who wish to continue receiving study drug after completion of this study. The option to continue receiving drug will be a separate stand alone continuation study.

34. Section 11.2 Evaluation of ABR before rVWF Prophylaxis and ABR under rVWF Prophylactic Treatment
    Description of Change: The text regarding bleeding episode history was updated to cover those subjects on-demand therapy prior to enrollment in the study.
    Purpose for Change: Administrative.

35. Section 11.4 Assessment of Efficacy for Treatment of Bleeding Episode; Section 21 References
    Description of Change: The table detailing the hemostatic efficacy rating scale was replaced with more detailed efficacy rating criteria for minor/moderate and major bleeding events. The corresponding reference was deleted from Section 21.
    Purpose for Change: Administrative.

36. Section 12.7 Vital Signs
    Description of Change: It was clarified that height and weight would be measured pre-infusion only.
    Purpose for Change: Administrative.

37. Section 12.9.16 Biobanking
    Description of Change: For this study, no back-up samples will be taken or stored long-term in a biobank for future analyses. This section describing biobanking procedures was removed from the protocol.
    Purpose for Change: Administrative.

38. Section 13.2.2 Full Analysis Dataset
    Description of Change: The definition of the Full Analysis Set was updated to include all subjects with available bleeding data gathered during prophylaxis, instead of those with a minimum of 6 months data.
    Purpose for Change: To allow estimation of ABR on all available bleeding data.

39. Section 13.4 Methods of Analysis
    Description of Change: Study success criteria were defined in the protocol.
    New text: The study success criteria are the objectives as stated in Section 7. "Treatment success" was defined as the extent of control of bleeding episodes achieved during this study.
    Purpose for Change: Administrative.

40. Section 13.4.2.3 Pharmacokinetic Analysis
    Description of Change: The proposed analysis was updated to reduce the number of descriptive statistics being reported.
    Purpose for Change: Administrative.

41. Section 13.4.2.4 Safety
    Description of Change: Some minor wording updates were made to clarify the timing of AEs and the assessments of causality for AEs and SAEs.
    Purpose for Change: Administrative.

INVESTIGATOR ACKNOWLEDGEMENT

RECOMBINANT VON WILLEBRAND FACTOR (rVWF)

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

CLINICAL TRIAL PHASE 3

AMENDMENT 1: 2016 APR 08

Replaces: ORIGINAL: 2014 FEB 19

OTHER PROTOCOL ID(s)
NCT Number: to be determined
EudraCT Number: 2016-001478-14
IND/IDE NUMBER: to be determined

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT

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A prospective, phase 3, open label, international multicenter study on efficacy and safety of prophylaxis with rVWF in severe von Willebrand Disease

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Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
[redacted], MD
[redacted], Global Clinical Development

CLINICAL STUDY PROTOCOL

PRODUCT: Recombinant Von Willebrand Factor (rVWF)

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 SHORT TITLE: rVWF IN PROPHYLAXIS

PROTOCOL IDENTIFIER: 071301

CLINICAL TRIAL PHASE 3

AMENDMENT 2: 2016 DEC 15

Replaces: AMENDMENT 1: 2016 APR 08

OTHER ID(s)
NCT Number: NCT02973087
EudraCT Number: 2016-001478-14
IND NUMBER: to be determined

Study Sponsor(s):	**Baxalta US Inc.**	**Baxalta Innovations GmbH**
	One Baxter Way	Industriestrasse 67
	Westlake Village, CA 91362	A-1221 Vienna
	UNITED STATES	AUSTRIA

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted]
Global Clinical Development Operations
Baxalta US Inc./Baxalta Innovations GmbH

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (e.g. investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) and suspected unexpected serious adverse events (SUSARs) to the ECs.

ALL SAEs, INCLUDING SUSARs, ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT.

Bleeding events that meet seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) should be reported on the SAE eCRF or SAE Report form as an SAE.

Drug Safety contact information: see SAE Report form
Refer to SAE Protocol Sections and the study team roster for further information.

For definitions and information on the assessment of these events, refer to the following:

- AE, Section 12.1
- SAE, Section 12.1.1.1
- SUSARs, Section 12.1.1.2
- Assessment of AEs, Section 12.1.2

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	Recombinant von Willebrand factor (rVWF)
Name(s) of Active Ingredient(s)	Recombinant von Willebrand factor (rVWF)
CLINICAL CONDITION(S)/INDICATION(S)	
Subjects with severe von Willebrand disease (VWD) requiring prophylactic treatment with coagulation factor replacement	
PROTOCOL ID	071301
PROTOCOL TITLE	A prospective, phase 3, open-label, international multicenter study on efficacy and safety of prophylaxis with rVWF in severe von Willebrand disease
Short Title	rVWF in prophylaxis
STUDY PHASE	Ph3
PLANNED STUDY PERIOD	
Initiation	2016 JUN
Primary Completion	2018 Q1
Study Completion	2018 Q1
Duration	22 months
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
The purpose of this phase 3 study is to investigate the efficacy and safety, including immunogenicity and thrombogenicity, and [redacted] of prophylactic treatment with rVWF in subjects with severe VWD.	
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 and to compare it to the subject's historical ABR for spontaneous bleeding episodes during on-demand treatment.	
Secondary Objectives	
Secondary Objectives are • Additional efficacy assessments of prophylactic treatment • Safety and immunogenicity • Pharmacokinetics (PK) • Efficacy of the treatment of bleeding episodes	
Exploratory Objectives	
[redacted]	

STUDY DESIGN	
Study Type/ Classification/ Discipline	Efficacy and Safety
Control Type	No control
Study Indication Type	Prophylaxis and treatment of bleeding episodes
Intervention model	Single-group
Blinding/Masking	Open-label
Study Design	This is a phase 3, prospective, open-label, non-randomized, international multicenter study evaluating efficacy, safety, including immunogenicity and thrombogenicity, and [redacted] of prophylactic treatment regimen with rVWF for subjects with severe VWD. Subjects will be offered the option to continue to receive BAX111 in a long-term continuation study.
Planned Duration of Subject Participation	Approximately 15 months
Primary Outcome Measure	
Efficacy • Prospectively recorded ABR for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF and the subjects' historical ABR for spontaneous bleeding episodes during on-demand treatment.	
Secondary Outcome Measure(s)	
Efficacy • Number (proportion) of subjects with reduction of ABR for spontaneous (not related to trauma) bleeding episodes during prophylaxis relative to the subjects' own historical ABR during on-demand treatment • Number (proportion) of subjects with 0 bleeds during prophylactic treatment with rVWF • Number of infusions and total weight adjusted consumption of rVWF and ADVATE (recombinant factor VIII/rFVIII) per month and per year during on-demand treatment **Safety** • Adverse events (AEs) • Incidence of thromboembolic events • Incidence of severe hypersensitivity reactions • Development of neutralizing antibodies to VWF and FVIII • Development of total binding antibodies to VWF and FVIII • Development of antibodies to Chinese hamster ovary (CHO) proteins, mouse immunoglobulin G (IgG) and rFurin **Pharmacokinetic** • Incremental recovery (IR), terminal half-life ($T_{1/2}$), mean residence time (MRT), area under the curve/dose (AUC/dose), area under moment curve/dose (AUMC/dose), volume of distribution at steady state (Vss) and clearance (CL) based on Von Willebrand factor Ristocetin cofactor activity (VWF:RCo), Von Willebrand factor antigen (VWF:Ag), Von Willebrand collagen binding activity (VWF:CB), INNOVANCE VWF Ac (exploratory assay) and time course (72 hours) of FVIII clotting activity (FVIII:C) levels.	

Efficacy of the treatment of bleeding episodes • Number of infusions of rVWF and ADVATE (rFVIII) per spontaneous bleeding episode • Number of infusions of rVWF and ADVATE (rFVIII) per traumatic bleeding episode • Weight-adjusted consumption of rVWF and ADVATE (rFVIII) per spontaneous bleeding episode • Weight-adjusted consumption of rVWF and ADVATE (rFVIII) per traumatic bleeding episode • Overall hemostatic efficacy rating at resolution of bleed	
Exploratory Outcome Measures	
[redacted]	
INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**Dosage form**: lyophilized powder and solvent for solution for injection **Dosage frequency**: Prophylactic Treatment Subjects transitioning from on-demand treatment will be infused twice weekly with BAX 111 (rVWF) at doses of 50 ± 10 IU/kg rVWF:RCo. Dosage may be individualized within this range based on: • the PK data • type and severity of bleeding episodes the subject has experienced in the past • monitoring of appropriate clinical and laboratory measures Any further adjustment will have to be agreed with the sponsor in advance. Treatment of Bleeding Episodes: Dosage must be individualized based on the subject's weight, type and severity of bleeding episode and monitoring of appropriate clinical and laboratory measures. In general, an initial dose of 40-60 IU/kg VWF:RCo with 30-45 IU rFVIII [ADVATE]/kg) is recommended (rVWF:rFVIII ratio of 1.3:1: ± 0.2). In cases of major bleeding episodes, a dose of up to 80 IU/kg VWF:RCo may be infused. Subsequent doses, if necessary, will be administered with or without ADVATE to maintain VWF:RCo and FVIII levels for as long as deemed necessary by the investigator. **Mode of Administration:** intravenous
SUBJECT SELECTION	
Targeted Accrual	Approximately 18 subjects to achieve 15 evaluable subjects with severe VWD
Number of Groups/ Arms/ Cohorts	Single-group

Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding:
   a. Type 1 (VWF:RCo <20 IU/dL) or,
   b. Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2M or,
   c. Type 3 (VWF:Ag ≤3 IU/dL).
2. Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.
3. Subject currently receiving on-demand treatment for whom prophylactic treatment is recommended according to standard of care at the center.
4. Has ≥3 documented spontaneous bleeds requiring VWF treatment during the past 12 months
5. Availability of records to reliably evaluate type, frequency and treatment of bleeding episodes during 12 months of on-demand treatment prior to enrollment.
6. Subject is ≥18 years old at the time of screening and has a body mass index ≥15 but <40 kg/m^2.
7. If female of childbearing potential, subject presents with a negative blood/urine pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.
8. Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

Subjects who meet ANY of the following criteria are not eligible for this study:

1. The subject has been diagnosed with Type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD (e.g., qualitative and quantitative platelet disorders or elevated prothrombin time (PT)/international normalized ratio [INR] >1.4).
2. The subject has received prophylaxis treatment in the 12 months prior to screening (including those who received treatment once a month for menorrhagia but were not treated for any other bleeds).
3. The subject is currently receiving prophylaxis treatment.
4. The subject has a history or presence of a VWF inhibitor at screening.
5. The subject has a history or presence of a FVIII inhibitor with a titer ≥0.4 BU (by Nijmegen modified Bethesda assay) or ≥0.6 BU (by Bethesda assay).
6. The subject has a known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins.
7. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
8. The subject has a medical history of a thromboembolic event.
9. The subject is HIV positive with an absolute Helper T cell (CD4) count <200/mm^3.
10. The subject has been diagnosed with significant liver disease as evidenced by any of the following: serum alanine aminotransferase (ALT) 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).
11. The subject has been diagnosed with renal disease, with a serum creatinine level ≥2.5 mg/dL.
12. The subject has a platelet count <100,000/mL at screening.
13. The subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to signing the informed consent.

14. The subject is pregnant or lactating at the time of enrollment.
15. Patient has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
16. The subject has participated in another clinical study involving another investigational product (IP) or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
17. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
18. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
19. The subject has a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
20. The subject is in prison or compulsory detention by regulatory and/or juridical order
21. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.

Delay criteria

1. If the subject presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) the screening visit will be postponed until the subject has recovered.

STATISTICAL ANALYSIS

Sample Size Calculation

The determination of the sample size for this study is not based on strict statistical considerations. The sample size of a subset of at least 15 subjects with severe VWD, 5 of whom must have Type 3 VWD, is based on the Guideline on the Clinical Investigation of Human Plasma Derived von Willebrand Factor Products (CPMP/BPWG/220/02).[1]

Planned Statistical Analysis

Primary Outcome Measure:

The statistical analysis will provide descriptive summaries.

The prospectively recorded annualized bleeding rate (ABR) of spontaneous (not related to trauma) bleeding episodes during prophylactic treatment will be assessed using negative binomial distribution. Mean ABR of spontaneous bleeding episodes together with the corresponding 95% two-sided confidence intervals (CIs) will be reported for the prospective counts as well as those based on historical data.

Secondary Outcome Measures:

Efficacy:

For the number of infusions and for the total weight adjusted consumption of rVWF and ADVATE per month and per year during on-demand treatment for bleeding episodes, summary statistics will be carried out.

For the number (proportion) of subjects with reduction of ABR relative to historic ABR as well as for the number (proportion) of subjects with 0 bleeds, proportions and corresponding 95% two-sided CIs will be performed.

The cause, type, localization and severity of bleeding episodes will also be recorded and summarized.

Efficacy of the Treatment of Bleeding Episodes:

For the number of infusions of rVWF and ADVATE per bleeding episode, for the weight adjusted consumption of rVWF and ADVATE per bleeding episode as well as for the overall hemostatic efficacy rating at resolution of bleed, summary statistics will be carried out.

The severity and localization of bleeding episodes will also be recorded and summarized. Bleeding episodes should be organized by where they occur in addition to whether they occurred spontaneously or due to a traumatic event.

Pharmacokinetic:

The PK parameters AUC_{0-72h}/Dose, $AUC_{0-\infty}$/Dose, $AUMC_{0-\infty}$/Dose, MRT (mean residence time), CL (clearance), IR (incremental recovery), $T_{1/2}$ (elimination phase half-life), V_{ss} (Volume of distribution at steady state), C_{max} (maximum concentration) and T_{max} (time to reach the maximum concentration) will be summarized by mean, standard deviation and the corresponding 90% CIs, median, Q1, Q3, IQR and range.

Descriptive statistics will be used to summarize VWF:RCo levels for each nominal time point on the PK curve.

For all subjects concentration vs. time curves will be prepared.

Safety:

The number of subjects who experienced SAEs and the number of SAEs will be tabulated. In addition, the number of subjects who experienced AEs assessed as related to IP by the investigator and by the sponsor, and the number of IP-related AEs will be tabulated and subcategorized for thromboembolic events, neutralizing and total binding antibodies to VWF and FVIII, and hypersensitivity reactions by severity. Additionally, antibodies to Chinese hamster ovary (CHO) proteins, antibodies to mouse immunoglobulin G (IgG) and antibodies to rFurin.

A listing of all AEs will be presented by subject identifier, age, sex, preferred term and 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. An overview table for AEs will be provided, presenting the number of AEs, the number of subjects with AEs and the corresponding percent of subjects in total and by seriousness and relationship to study treatment. An additional summary table will present the total number of (mild, moderate, severe) AEs by system organ class and preferred term with relationship to IP.

<u>Exploratory Outcome Measures:</u>

[redacted]

4. TABLE OF CONTENTS

Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABR	Annualized bleeding rate
ADAMTS13	A Disintegrin And Metalloproteinase with a Thrombospondin type 1 motif, number 13
AE	Adverse event
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC0-∞	Area under the plasma concentration /time curve from time 0 to infinity
$AUC_{0\text{-}72h}$/Dose	Area under the plasma concentration/time curve from time 0 to 72 hours post-infusion/dose
$AUC_{0\text{-}\infty}$/Dose	Area under the plasma concentration/time curve from time 0 to infinity/dose
AUC/Dose	Area under the curve/dose
AUMC	Area under moment curve
$AUMC_{0\text{-}\infty}$/Dose	Area under the first moment curve from time 0 to infinity/dose
aPTT	Activated partial thromboplastin time
B19V	Parvovirus B19
BILI	Bilirubin
BP	Blood pressure
BU	Bethesda Unit
BUN	Blood urea nitrogen
BW	Body weight
CAM	Cell adhesion molecule
CB	Collagen binding activity
CBC	Complete blood count
CD4	Helper T cell
CHO	Chinese hamster ovary
CI	Confidence interval
Cl	Chloride
CL	Clearance
C_{max}	Maximum plasma concentration
CR	Creatinine
CTA	Clinical Trial Agreement
eCRF	Electronic case report form
DMC	Data monitoring committee

Abbreviation	Definition
DIC	Disseminated intravascular coagulation
DVT	Deep vein thrombosis
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
FVIII	Factor VIII
FVIII:C	Factor VIII clotting activity
GCP	Good Clinical Practice
GI	Gastrointestinal
Glu	Glucose
GPIb	Glycoprotein Ib
HAMA	Human anti- mouse antibodies
HAV	Hepatitis A virus
HB	Hepatitis B
HBs	Hepatitis B surface
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
[redacted]	[redacted]
HRP	Horseradish peroxidase
IB	Investigator's brochure
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INR	International normalized ratio
IP	Investigational product
IQR	Interquartil range
IR	Incremental recovery

Abbreviation	Definition
i.v.	Intravenous
K	Potassium
k.o.	Knock out
LDH	Lactate Dehydrogenase
Na	Sodium
NMC	Non-medical complaint
NOAEL	No observed adverse effect level
MRI	Magnetic resonance imaging
MRT	Mean residence time
pdVWF	Plasma derived VWF product
pdVWF/FVIII	Plasma derived VWF product containing fractions of FVIII
PBAC	Pictorial Blood Assessment Chart
PCR	Polymerase Chain Reaction
PEF	Peak expiratory flow
PK	Pharmacokinetic
PKFAS	Pharmacokinetic Full Analysis Set
PKPPAS	Pharmacokinetic Per Protocol Analysis Set
PP	Per protocol
PT	Prothrombin time
Q1, Q3	Quartile
rFVIII	Recombinant factor VIII
rVWF	Recombinant von Willebrand factor
RBC	Red blood cell count
SAE	Serious adverse event
SAER	Serious adverse event report
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
[redacted]	[redacted]
SIC	Subject identification code
sP-selectin	Soluble P-selectin
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Elimination phase half life
TIA	Transient ischemic attack
Tmax	Time to reach the maximum concentration

Abbreviation	Definition
TTP	Thrombotic thrombocytopenic purpura
ULMW	Ultra-large molecular weight
ULN	Upper limit of normal
Vss	Volume of distribution at steady state
[redacted]	[redacted]
VTE	Venous thromboembolism (VTE)
VWD	von Willebrand disease
VWF	Von Willebrand factor
VWF:Ag	Von Willebrand factor antigen
VWF Ac	VWF activity measured INNOVANCE VWF Ac assay
VWF:CB	Von Willebrand Factor collagen binding
VWF:RCo	Von Willebrand factor: Ristocetin cofactor activity
WBC	White blood cell

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

Baxalta US Inc. (hereafter referred to as Baxalta or sponsor) has developed a human recombinant von Willebrand Factor (rVWF), which is co-expressed with recombinant factor VIII (rFVIII) in a Chinese hamster ovary (CHO) cell line and separated during the subsequent downstream process. To address concerns regarding the risk of transmission of blood-borne pathogens that may be introduced by human plasma, no exogenously added raw materials of human or animal origin are employed in the cell culture, purification, or formulation of the final container product. The only proteins present in the final container product other than rVWF are trace quantities of murine immunoglobulin (IgG, from the immunoaffinity purification), host cell (i.e., CHO) protein, rFurin (used to further process rVWF). rVWF is intended for the treatment of von Willebrand disease (VWD).

rVWF has been developed under the Baxalta internal code BAX111 and is used as investigational product (IP) in this study. rVWF may be used with or without ADVATE (rFVIII) for the treatment of bleeding episodes (see Section 8.7.4.4). See Section 8.7 for further information on the IPs and their usage in this study. A detailed description of rVWF is also provided in the Investigator's Brochure (IB).

rVWF was granted licensure in the United States in December 2015 under the brand name VONVENDI for the on-demand treatment and control of bleeding episodes in adults diagnosed with VWD; as of the date of this protocol VONVENDI is not yet available on the market.

6.2 Clinical Condition/Indication

Von Willebrand Factor (VWF) is a large multimeric glycoprotein with a molecular weight that varies from 500 to 20,000 kDa. VWF is normally found in plasma and produced in the alpha-granules of platelets and in endothelial cell organelles known as the Weibel-Palade bodies. VWF mediates platelet adhesion and aggregation at sites of vascular injury, one of the key functions in primary hemostasis. VWF also serves to stabilize coagulation factor VIII (FVIII), where FVIII is an essential cofactor of secondary hemostasis, which leads to fibrin clot formation.[2] Qualitative and/or quantitative deficiencies of VWF lead to a highly variable bleeding diathesis known as VWD, the most common of the hereditary coagulation factor deficiencies. Penetrance of VWD is highly variable, with only a small fraction of mildly affected patients displaying clinical symptoms or a family history of a bleeding diathesis.

The current biochemical-based classification distinguishes disorders arising from partial quantitative (type 1), qualitative (type 2), or virtually complete (type 3) deficiencies of VWF. Up to 70% of VWD patients are diagnosed with type 1 VWD, which may also be associated with minor functional defects in the molecule. In general, patients with type 1 VWD display mild clinical symptoms. Approximately 20 to 30% of VWD patients are diagnosed with type 2 VWD. Type 2 VWD is further divided into 4 subtypes (A, B, N, and M), reflecting distinct classes of functional abnormalities. These defects result in abnormal functional and/or multimeric distribution patterns that facilitate their diagnosis. The bleeding diathesis is usually moderate and primarily affects the mucosal tissues. Type 2N VWD patients are sometimes misdiagnosed as mild hemophilia A. Finally, approximately 1% percent of VWD patients exhibit a total or near total absence of VWF, which is classified as type 3 VWD. The incidence of type 3 VWD is estimated at 0.5-1.0 x 10^6. This type is also associated with a very low FVIII level (typically <5%) because the VWF carrier function for FVIII is lost. Replacement of VWF alone stabilizes endogenous FVIII, resulting in hemostatic levels within several hours post-infusion. Published results from studies of a plasma-derived VWF concentrate demonstrated an increase of FVIII at an approximate rate of 5.8 ± 1 IU dL^{-1} h^{-1}.[3] Type 3 VWD patients display severe hemorrhagic symptoms with bleeding predominantly in mucosal tissues, muscle and joints. All VWD patients, particularly those with type 2 or type 3 VWD, are at an increased risk for life-threatening bleeding episodes.

6.3 The Role of Prophylaxis in the Management of VWD

The goals of long term prophylaxis in VWD are to maintain VWF and FVIII at sufficient levels to reduce the frequency and duration of bleeding episodes, the need for red blood cell transfusions, and the risk of complications, such as arthropathy.[4] In contrast to hemophilia, routine prophylaxis is not as established in VWD, although prophylaxis for patients with severe VWD have already been in use in Sweden during the 1950s.[5] In those early days of VWD treatment plasma FVIII concentrates containing VWF fractions were applied for replacement therapy, which then were followed by plasma derived VWF products containing fractions of FVIII (pdVWF/FVIII).

A Swedish cohort including 37 patients with type 3 VWD under prophylactic median treatment of 11 years (range 2 to 45 years) was retrospectively analyzed.[6;7] The doses used for prophylaxis, given once weekly for at least 45 weeks per year, were calculated based on 12 to 50 IU/kg body weight (BW) of FVIII clotting activity (FVIII:C) which approximately corresponded to 24-100 IU/kg von Willebrand factor: Ristocetin cofactor activity (VWF:RCo) considering that mainly Haemate with a known VWF:RCo/FVIII:C ratio of about 2 was used. An escalation of doses from 1 to 3 dose levels was allowed depending on the frequency and severity of bleeding episodes.

The results demonstrate that under long-term prophylaxis the number of bleeds could be reduced dramatically. Whereas the median value for bleeds per year was about 10 before prophylaxis this value could be reduced to less than 1 bleed per year during prophylaxis.

The benefit of prophylaxis for such indications was retrospectively also demonstrated in a cohort of Italian patients including type 3, 2A, 2M and type 1 patients. Prophylaxis was started after severe gastrointestinal or joint bleeding episodes and completely prevented bleeding episodes in 8 of these 11 patients and largely reduced the need of blood transfusions in the remaining 3. A regimen of 40 IU rVWF:RCo/kg was applied every other day or twice a week. A prospective study on prophylaxis, the PRO.WILL study, has been initiated in Italy.[8]

The results of a prospective study investigating the prophylaxis in children and young adults showed a significantly reduced bleeding frequency and bleeding score (3 vs. 0.07; 3 vs. 0. $p<0.001$) compared to the pre-prophylaxis values. The median dose was 40 (20-47) IU/kg VWF:RCo administered mainly twice weekly in 23 patients, 3 times a week in 7 patients and 4 times a week in 2 children.[9]

The VWD Prophylaxis Network initiated the VWD International Prophylaxis (VIP) trial to investigate the role of prophylaxis in patients with severe VWD including Type 1, 2, and 3. The dose of the factor replacement product was 50 IU /kgVWF:RCo. The frequency of the dose depended on the type of bleeding and could be increased from once weekly to twice weekly or 3 times per week. For the treatment of menorrhagia the dose of 50 IU/kg VWF:RCo was given on the first day of menses for 2 cycles. The frequency could be increased to Day 1 and 2 for 2 cycles or to Day 1, 2, and 3 of menses.

The study contains both retrospective and prospective study components. Results from the retrospective study component were published, including 61 subjects on prophylactic regimen in the past 6 months prior to enrollment or subjects with a history of prophylaxis over at least 6 month.[10] Differences in annualized bleeding rates (ABR) within individuals (during prophylaxis – before prophylaxis) were significant for those with primary indications of epistaxis ($P = 0.0005$), joint bleeding ($P = 0.002$) and gastrointestinal (GI) bleeding ($P = 0.001$). The difference in the group whose primary indication for treatment was abnormally heavy bleeding at menstruation ($n = 4$) was not significant ($P = 0.25$). The reduction of mucosal bleeding likely not only dependents on normal circulating levels of active VWF, but also on the presence of discrete concentrations of normal VWF inside the platelets and within endothelial matrices. The low subject number ($n=4$) and the treatment scheme for menorrhagia on Days 1, 2, and 3 of menses which might represent rather on-demand than prophylactic treatment may also account for the outcome in this study.

Results from the prospective study component were reported recently.[11] Eleven subjects completed the study. Six subjects had type 2A, and 5 subjects had type 3 VWD. Six subjects presented with epistaxis, 3 with GI bleeding, and 2 with joint bleeding. Seven subjects had dose escalation above the first level. Among the 10 subjects with evaluable bleeding log data, the use of prophylaxis decreased the median ABR from 25 to 6.1 (95% confidence interval [CI] of the rate difference: -51.6 to -1.7), and the median ABR was even lower (4.0; 95% CI: -57.5 to -5.3) when the subjects reached their final dosing level. The authors concluded that this was the first prospective study to demonstrate that prophylaxis with VWF concentrates is highly effective in reducing mucosal and joint bleeding rates in clinically severe VWD.

The results of the VIP study and previous investigations suggest that VWD patients with recurrent bleeding episodes and severe menorrhagia will benefit from a prophylactic VWF replacement therapy. There is evidence that up to 40% of patients with type 3 VWD experience joint bleeding which can lead to hemophilic arthropathy. Other potential indications for prophylaxis include patients with type 2A or 2B VWD with recurrent gastrointestinal bleeding, menorrhagia or frequent epistaxis.[4] Long-term prophylaxis for most patients with type 3 VWD and in some patients with type 1 or 2 VWD, depending on the pattern of bleeding, may be the treatment option of choice. Although the main experience with long-term prophylaxis is with secondary prophylaxis, primary prophylaxis starting at young age is recommended to prevent arthropathy in patients with severe VWD.[12]

However, further studies are needed to develop evidence-based guidelines for prophylactic treatment in VWD.

6.4 Population to be Studied

A total of approximately 18 eligible, adult subjects to achieve approximately 15 evaluable subjects with severe VWD are planned to be enrolled, of which a subset of at least 5 subjects will have type 3 VWD. Enrolled subjects (i.e., subjects who have signed the informed consent form) will be eligible to participate in the study if they meet all of the inclusion criteria (see Section 9.1) and none of the exclusion criteria (see Section 9.2).

6.5 Findings from Nonclinical and Clinical Studies

The following summarizes the key findings from relevant nonclinical studies as well as from the completed clinical studies **070701** (Phase 1 PK and safety in VWD), **071001** (Phase 3 safety and efficacy in the treatment of bleeding episodes in VWD), **071104** (Phase 1 safety and PK in hemophilia A), and **071401** (Phase 3, expanded access in a

single subject with VWD). Potential risks and efficacy of rVWF:ADVATE are summarized in the following sections. For additional information on nonclinical and clinical Phase 1 results refer to the rVWF IB.

6.5.1 Findings from Nonclinical Studies

6.5.1.1 Primary Pharmacodynamics

Efficacy of rVWF combined with ADVATE was shown in VWD animal models, which have also low endogenous FVIII levels. Time to occlusion and stable thrombus formation was assessed in the carotid occlusion model in VWD mice. The results demonstrated that rVWF in combination with ADVATE acted efficiently in a dose-dependent manner and had higher efficacy than rVWF alone or plasma derived (pd)VWF. These results were confirmed in an additional study assessing blood loss and survival in a tail tip bleeding model in VWD mice. In a VWD dog rVWF stabilized canine FVIII in the circulation and significantly reduced the bleeding time.

6.5.1.2 Safety Pharmacology

The anaphylactoid and thrombogenic potential of the co-infusion of ADVATE and rVWF and the co-infused product's effects on blood pressure, cardiac and respiratory function and parameters of coagulation activation were investigated in 4 in vivo studies in different animal models. Safety pharmacology studies in rats, guinea pigs, rabbits, and dogs revealed no risks for anaphylactoid and thrombogenic potential of ADVATE in combination with rVWF. All observations in safety pharmacology studies are considered to lie within the biological variability of animal models or occurred due to known species-specific anaphylactoid effects of excipients.

6.5.1.3 Pharmacokinetics

Pharmacokinetic studies of both rVWF alone and combined with human rFVIII (rVWF+ADVATE) were conducted in VWD mice, VWD dogs, VWD pigs, rats, and cynomolgus monkeys. Human rVWF stabilized the endogenous FVIII in VWD mice, VWD pigs, and VWD dogs. Furthermore, the hypotheses that the area under the curve (AUC) with rVWF alone and rVWF+ADVATE is not inferior to the AUC with pdVWF (Haemate P) was tested and confirmed statistically in normal rats. The pharmacokinetic (PK) characteristics of ADVATE were not affected by co-administration of rVWF in cynomolgus monkeys. The PK data in the FVIII knock out (k.o.) mice model are inconclusive and might not be relevant for the clinical situation. However, a stabilizing effect of VWF on FVIII could be shown in a double knock out model in a dose dependent manner.

6.5.1.4 Toxicology

Single dose toxicity studies were conducted in C57BL/6J-mice, VWD mice, rats, rabbits, and cynomolgus monkeys. Rats, rabbits, and cynomolgus monkeys showed no signs of toxicity. Signs of microthrombosis, an exaggerated pharmacological effect, were observed in mice. Mice are not capable of sufficiently cleaving the rVWF subunit as murine disintegrin and metalloproteinase with a thrombospondin type 1 motif, number 13 (ADAMTS13) does not decrease the ultra-large molecular weight multimers of rVWF.[13] The observed symptoms of microthrombosis are interpreted as a species-specific exaggerated pharmacological effect. Studies evaluating the safety of repeated administration of rVWF with or without ADVATE (daily over 14 days) were performed in a rodent (rat) and non-rodent (cynomolgus monkey) species. Reversible signs of exaggerated pharmacological effects (regenerative anemia, thrombocytopenia, and treatment-related histopathologic changes in the heart, liver, and spleen) were observed in rats that were administered 1400 U VWF:RCo/kg /day + 1080 IU ADVATE/kg/day intravenously once daily for 14 days. Also, these findings are interpreted as a species-specific exaggerated pharmacological effect due to the low susceptibility of human rVWF to cleavage by rodent ADAMTS13.[13] No toxicologically relevant changes were evident for clinical observations, body weight, feed consumption, ophthalmology, urinalysis, coagulation, and serum chemistry parameters, platelet aggregation, and gross pathology. rVWF combined with ADVATE was well tolerated in cynomolgus monkeys after daily intravenous (i.v.) (bolus) administration of 100 U VWF:RCo/kg rVWF combined with 77 IU/kg ADVATE over a period of 14 days. No adverse effects could be detected in this species. There were no signs of hemolysis, thrombosis, or thrombocytopenia after repeated intravenous application of rVWF with or without ADVATE. Therefore, 100 U VWF:RCo/kg/day rVWF with or without 77 IU/kg ADVATE was considered the no observed adverse effect level (NOAEL) in this study, which was the highest dose tested. Anti-drug antibodies, however, were formed in both species and resulted in a significant reduction in drug exposure after 14 applications as compared to a single application. These antibodies substantially reduced the systemic exposure to the test substance as compared to a single dose administration. No adverse effects due to antibody formation were observed in both species.
rVWF combined with ADVATE was well tolerated locally and no genotoxic potential was evident after 2 in vitro and 1 in vivo genotoxicity study. A study on the influence of co-administration of VWF and ADVATE on the immunogenicity of ADVATE in 3 different hemophilic mouse models (E17 hemophilic Balb/c mice, E17 hemophilic C57BL/6J mice, and E17 hemophilic human F8 transgenic mice) showed that rVWF does not negatively impact the immunogenicity of ADVATE in any of the three different hemophilic mouse models.

6.5.2 Findings from Clinical Studies

Two phase 1 studies with rVWF either alone or co-administrated with ADVATE in patients with VWD **070701** and Hemophilia A **071104** and 1 phase 3 study with rVWF in patients with VWD **071001** have been conducted and the results were analyzed and evaluated. Details on study design, populations enrolled, and safety and efficacy outcomes of these 2 phase 1 studies are presented in Section 6.5.2.1 and Section 6.5.2.2, and the phase 3 study in Section 6.5.2.3. Information on a single subject with VWD in Study **071401** is presented in Section 6.5.2.4.

Refer to rVWF IB for periodic updates from other rVWF studies.

6.5.2.1 Study 070701

Phase 1 clinical study **070701** was a multicenter, controlled, randomized, single-blind, prospective 3-step, dose escalation study to investigate safety, tolerability, and PK of rVWF combined at a fixed ratio with ADVATE (VWF:RCo/FVIII:C of 1.3 ± 0.2:1) in adults with severe VWD.[14] Subjects were enrolled in sequential cohorts in a dose escalating manner: Cohort 1, 2, and 3 received a single intravenous infusion of rVWF:ADVATE at the following doses: 2 IU/kg VWF:RCo (Cohort 1), 7.5 IU/kg VWF:RCo (Cohort 2), and 20 IU/kg VWF:RCo (Cohort 3). Subjects in Cohort 4 received a single intravenous infusion of rVWF:ADVATE and pdVWF/ADVATE at 50 IU/kg VWF:RCo in random order.

The primary endpoint was the tolerability and safety after single dose injections of rVWF:ADVATE at 2, 7.5, 20, and 50 IU/kg VWF:RCo for up to 30 days after the last IP infusion. The data generated in this phase 1 study suggest that rVWF:ADVATE up to the highest investigated dose of 50 IU/kg VWF:RCo is well tolerated and safe in adults with severe VWD. No thrombogenic risk or TTP-like syndrome was observed, and no neutralizing antibodies to VWF or FVIII were identified. There were no deaths or other serious adverse reactions, and no infusions were interrupted or stopped due to an AE. Overall, the reported AE profile was similar between the recombinant and plasma-derived concentrates.

Secondary endpoints were the PK assessment of VWF:RCo, von Willebrand factor antigen (VWF:Ag) and multimeric composition of rVWF as well as FVIII:C at standardized time points after single injections of rVWF:ADVATE and pdVWF:FVIII.

The median VWF:RCo half-life ($T_{1/2}$) of rVWF at the 50 IU/kg dose was 16 hours. $T_{1/2}$ with pdVWF:FVIII at the same dose level appeared shorter at 12.58 hours, however, the limits of the 90% CI were similar (11.73 to 17.7 hours vs. 11.87 to 18.03 hours).

The median half-lives of VWF:RCo were shorter with the lower investigated doses: 7.13 hours and 13.23 hours with the 7.5 IU/kg and 20 IU/kg doses, although these data were derived from a much smaller number of subjects.

In consequence of the missing ADAMTS13 cleavage, ultra-large molecular weight (ULMW) multimers are contained in the rVWF final product. The immediate cleavage of these ultra-large multimers by ADAMTS13 upon release into the circulation could be demonstrated applying sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE)/Immunoblot with polyclonal anti-VWF antibodies to detect the resulting rVWF subunit cleavage fragments.

Overall the data generated in this phase 1 study suggest that rVWF:ADVATE is well tolerated and safe in adults with severe VWD.

6.5.2.2 Study 071104

This study was a prospective, uncontrolled, non-randomized, multicenter proof of concept study to assess safety and PK of the addition of rVWF to ADVATE treatment in 12 evaluable subjects with severe hemophilia A. All subjects underwent 3 PK analyses: the first after infusion with ADVATE alone, the second after infusion with ADVATE plus 10 IU/kg rVWF and the third after infusion with ADVATE plus 50 IU/kg rVWF.

The PK analysis was performed at intervals of approximately 8 to 14 days. Before each infusion for PK assessment, there was a wash-out period of at least 5 days and the subjects were not actively bleeding.

Primary outcome measures indicate that co-administration of rVWF slightly sustain ADVATE activity with the highest observed ADVATE half-life of 13.74 h (CI 11.44 to 16.52) after co-infusion of 50 IU/kg ADVATE plus 50 IU/kg rVWF:RCo.

The highest improvement in ADVATE circulating half-life was observed in subjects with VWF:Ag levels below 100% which indicates an association between baseline VWF:Ag levels and ADVATE half-life increase.

No treatment related adverse events (AEs) or serious adverse events (SAEs) were reported. No subject withdrew due to an AE and there were no deaths. No binding antibodies to VWF, CHO, and rFurin were detectable in the confirmatory assay and no signs of a hypersensitivity to rVWF or ADVATE antigen were observed. Laboratory values over time did not indicate any potential safety risk for hemophilia A patients treated with rVWF and ADVATE in combination.

In summary, the data indicate that rVWF co-administered with ADVATE up to the highest dose of 50 IU/kg VWF:RCo is well tolerated and safe in hemophilia A patients.

6.5.2.3 Study 071001

This was a phase 3, multicenter, open-label, part-randomized clinical study to assess the PK, safety, and efficacy of rVWF:rFVIII and rVWF in the treatment of bleeding episodes in adult subjects with severe type 3 and severe non-type 3 VWD.[15] A total of 49 subjects were enrolled (signed informed consent) and screened, 18 subjects were randomized (Arm 1 and Arm 2 [PK 50] only), 37 subjects were treated with IP (all study arms), and 30 subjects completed the study.

The study consisted of 2 parts (Part A and Part B). Part A consisted of PK assessments alone (Arm 2: PK50 only [without treatment of bleeding episodes]), or PK assessments (Arm 1: PK50 and Arm 3: PK80) plus on-demand treatment period(s) of 6 months for bleeding episodes, or on-demand treatment for bleeding episodes only (Arm 4). Subjects receiving treatment for PK assessments and/or bleeding episodes in Part A were to be entered into Part B to continue on-demand treatment for bleeding episodes for 6 additional months for a total of 12 months in the study.

The primary outcome measure was the number of subjects with "treatment success" (extent of control of bleeding episodes), which was defined as a mean efficacy rating score of <2.5 for a subject's IP-treated bleeding episodes during the study. The rate of subjects with treatment success was 100% (Clopper-Pearson exact 90% CI: 84.7 to 100.0) for bleeds where the assessments were made prospectively and excluding GI bleeds. Sensitivity analyses confirmed the results of the primary analysis.

Crossover results at 50 IU/kg VWF:RCo showed that the PK profile for rVWF VWF:RCo was independent of administration alone or with rFVIII (ADVATE) ($T_{1/2}$: 19.4 hours for rVWF and 16.6 hours for rVWF:rFVIII; IR: 1.8 U/dL per IU/kg infused for both rVWF and rVWF:rFVIII; MRT: 26.7 hours for rVWF and 25.2 hours for rVWF:rFVIII). FVIII levels increased substantially with a median peak at 24 hours of 111.0 U/dL for rVWF:rFVIII and 86.0 U/dL after rVWF alone, indicating that rVWF induces a sustained increase in endogenous FVIII activity. The rVWF PK profile was comparable at 50 IU/kg and 80 IU/kg VWF:RCo, and repeated PK at 80 IU/kg VWF:RCo showed close agreement between pretreatment and end-of-study results.

Further analysis of the PK data from the **071001** study supports the initial use of 50 IU/kg twice weekly for prophylaxis dosing in the present study for those subjects who are moving from on-demand to prophylaxis. Using 50 IU/kg for PK measurements, subjects in the **071001** study exhibiting a $T_{1/2}$ for rVWF of 14, 16, or 19 hours had BAX111 plasma concentrations at 72 hours after administration of 2.55, 4.01, and 6.49% above baseline, respectively, and plasma concentrations at 96 hours after administration of 0.78, 1.40, and 2.71% above baseline, respectively. Subjects who have significant spontaneous bleeding while on twice weekly prophylaxis will have their regimen increased to 50 IU/kg 3 times per week (see Section 8.7.4.2).

A total of 125 AEs occurred in 25/37 (67.7%) subjects (62/318 infusions [19.5%]) during or after infusion with IP. Of these, 116/125 were non-serious (all mild or moderate; none were severe), and 9 SAEs were reported in 7 subjects. Of 125 total AEs, 38 were temporally associated with IP; 8 AEs were considered causally related to IP: 6 non-serious related AEs (tachycardia, infusion site paraesthesia, electrocardiogram [ECG] t-wave inversion, dysgeusia, generalized pruritis, and hot flush) occurred in 4 subjects, and 2 related SAEs (chest discomfort and increased heart rate) occurred in 1 subject. No deaths occurred during this study.

None of the subjects developed anti-VWF or anti-FVIII neutralizing antibodies and no binding antibodies to VWF or rFurin, or antibodies against CHO protein or anti-Murine IgG were observed. No clinical or subclinical signs or symptoms of a thrombogenic event were observed in this study. Following an initial increase in ultralarge VWF multimers after administration of rVWF, a notable decrease in the proportion of large VWF multimers occurred between 12 and 24 hours post infusion, due to degradation by the endogenous ADAMTS13 followed by a continued decline until the end of the 96-hour follow-up period.

Overall, the data support the safe and effective use of rVWF with or without FVIII (ADVATE) in the treatment of bleeds in patients with VWD.

6.5.2.4 Study 071401: Single Subject with von Willebrand Disease

One subject who exhibited allergic reactions to currently marketed pdVWF products was treated in the single-subject study **071401** with rVWF only for the bleed treatment of continued hematuria, and for biopsy and surgical resection of a left-kidney mass.

For the initial rVWF infusion, the subject received a test dose of 5% of the total dose of 60 IU/kg rVWF:RCo at an infusion rate of 1 mL/min. After a 10 to 15-minute observation period, no adverse symptoms or signs were noted and the subject received

the remaining 95% of the total dose. The subject was monitored for any signs of an allergic reaction, and none were noted. Treatment with rVWF every 12 to 24 hours was to continue at the discretion of the investigator based on VWF levels and clinical symptomatology. The subject had an excellent response and recovery, which allowed for daily dosing of rVWF and, within 24 hours, the subject's bleeding had stopped. Daily dosing of rVWF was maintained and the subject received his last dose on [redacted].

The subject also received rVWF for 7 days for prophylaxis for surgery (surgical resection of a left-kidney mass). The subject experienced no hemorrhagic complications and no AEs that were considered related to the use of rVWF.

6.6 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

Current treatment of VWD patients relies on desmopressin and VWF products manufactured from pooled human plasma. Human VWF produced by recombinant technology could offer a new perspective in treatment of VWD. The benefit for the individual subject is anticipated to be significant during this clinical study. He/she may benefit from a product that minimizes excessive FVIII administration. Variations in VWF multimeric composition may lead to variability with respect to treating or preventing bleeds in VWD subjects, especially mucosal bleeds which are especially problematic. rVWF product manufactured by Baxalta consistently contains ultra-large molecular weight (ULMW) VWF multimers due to the fact that the product has not been exposed to ADAMTS13. The initial presence of these ULMW VWF multimers, which are subsequently cleaved by the subject's endogenous ADAMTS13, may result in improved platelet and collagen binding and therefore provide more predictable treatment outcomes.

By using a recombinant product, the risk of contamination with blood derived viruses or variant Creutzfeldt-Jakob Disease associated with the use of products of human or animal origin has been virtually eliminated. At this stage of product development, the key societal benefit is a better understanding of advanced treatment options for VWD and enhanced product availability.

These benefits outweigh the following potential risks of rVWF:

- allergic-type hypersensitivity reactions as with any intravenous protein product
- the occurrence of thromboembolic events
- the development of neutralizing antibodies to VWF

Refer to the IB for further details on benefits and risks of the IP.

6.7 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives 2001/20/EC and 2005/28/EC, and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of this phase 3 study is to investigate the efficacy and safety, including immunogenicity and thrombogenicity, and [redacted] of prophylactic treatment with rVWF in subjects with severe VWD.

7.2 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 and to compare it to the subject's historical ABR for spontaneous bleeding episodes during on-demand treatment.

7.3 Secondary Objectives

Secondary Objectives are:

- Additional efficacy assessments of prophylactic treatment
- Safety and immunogenicity
- Pharmacokinetics
- Efficacy of the treatment of bleeding episodes

7.4 Exploratory Objectives

7.4.1 [redacted]

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

8. STUDY DESIGN

8.1 Brief Summary

8.2 Overall Study Design

This is a prospective, open label, uncontrolled, non-randomized, international, multicenter phase 3 study to evaluate efficacy, safety, including immunogenicity and thrombogenicity, and [redacted] of a prophylactic treatment regimen with rVWF in patients with severe VWD.

Subjects transitioning either from on-demand treatment or from prophylactic treatment will be infused twice weekly with BAX 111 (rVWF) at doses of 50 ± 10 IU/kg rVWF:RCo. The dose may be adjusted within this range based on the PK data, subject's history of bleeding episodes, and the results from clinical and laboratory assessments (see Section 8.7.4.2).

The overall duration of prophylactic treatment per subject will be 12 months.

During this period any bleeding episodes requiring substitution therapy with VWF concentrate to control bleeding will be treated with rVWF with or without ADVATE. The dose will be according to the bleeding severity and it will be adjusted to the clinical response (see Section 8.7.4.4.2).

The overall study design is illustrated in Figure 1.

8.3 Duration of Study Period(s) and Subject Participation

The overall duration of the study is approximately 22 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The subject participation period is approximately 15 months from enrollment to completion (i.e, last study visit), unless the subject is prematurely discontinued.

Subjects will be offered the option to continue to receive BAX111 in a long-term continuation study.

8.4 Outcome Measures

8.4.1 Primary Outcome Measure

The primary outcome measure is

- Efficacy:
  - Prospectively recorded ABR for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF and the subjects' historical ABR for spontaneous bleeding episodes during on-demand treatment.

8.4.2 Secondary Outcome Measures

8.4.2.1 Efficacy

- Number (proportion) of subjects with reduction of ABR for spontaneous (not related to trauma) bleeding episodes during prophylaxis relative to the subjects' own historical ABR during on-demand treatment
- Number (proportion) of subjects with 0 bleeds during prophylactic treatment with rVWF
- Number of infusions and total weight adjusted consumption of rVWF and ADVATE per month and per year during on-demand treatment

8.4.2.2 Safety

- AEs
- Incidence of thromboembolic events
- Incidence of severe hypersensitivity reactions
- Development of neutralizing antibodies to VWF and FVIII
- Development of total binding antibodies to VWF and FVIII
- Development of antibodies to Chinese hamster ovary (CHO) proteins, mouse immunoglobulin G (IgG) and rFurin

8.4.2.3 Pharmacokinetics

- Incremental recovery (IR), terminal half-life ($T_{1/2}$), mean residence time (MRT), area under the curve/dose (AUC/dose), area under moment curve/dose (AUMC/dose), volume of distribution at steady state (Vss) and clearance (CL) based on Von Willebrand factor Ristocetin cofactor activity (VWF:RCo), Von Willebrand factor antigen (VWF:Ag), Von Willebrand collagen binding activity (VWF:CB), INNOVANCE VWF Ac (exploratory assay) and time course (72 hours) of FVIII clotting activity (FVIII:C) levels.

8.4.2.4 Efficacy of the Treatment of Bleeding Episodes

- Number of infusions of rVWF and ADVATE (rFVIII) per spontaneous bleeding episode
- Number of infusions of rVWF and ADVATE (rFVIII) per traumatic bleeding episode
- Weight-adjusted consumption of rVWF and ADVATE (rFVIII) per spontaneous bleeding episode
- Weight-adjusted consumption of rVWF and ADVATE (rFVIII) per traumatic bleeding episode
- Overall hemostatic efficacy rating at resolution of bleed

8.4.3 Exploratory Outcomes Measure

[redacted]

8.5 Randomization and Blinding

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

8.6 Study Stopping Rules

This study will be stopped if 1 or more of the following criteria are met:

1. Two subjects develop a thromboembolic event

2. Two subjects develop severe hypersensitivity reactions (e.g., clinically significant localized urticaria, generalized urticaria, wheezing, or anaphylaxis); or infusion related tightness of the chest or hypotension
3. Two subjects develop signs and symptoms, suggestive of a thrombotic thrombocytopenic purpura-like syndrome (subjects with type 2B VWD developing thrombocytopenia or changes of the platelet count as described below, will be evaluated on case by case, whether they need to be accounted for), such as
    - A drop in platelet count of 50% of subject's baseline or less than 100.000 per microliter
    - 3-fold increase in lactate dehydrogenase (LDH)
    - Impaired renal function as determined by:
        - Creatinine increase of 1.5-fold from baseline levels
        - Blood urea nitrogen (BUN) increase from normal levels to a level > 60 mg/dL
4. Any subject has abnormal liver function:
    - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations >5 times upper limit of normal (ULN) in the absence of a concomitant bilirubin increase
    - ALT and/or AST elevations >3 times ULN in the presence of a total bilirubin increase >2 times ULN or an international normalized ratio (INR) >1.5 without findings of cholestasis or other alternate etiology to explain the elevations (i.e., "Hy's Law cases")
    - ALT and/or AST elevations >3 times ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
5. Two subjects develop rVWF neutralizing antibodies

The study may be stopped at any time by the sponsor.

The sponsor ultimately will decide whether to terminate, temporarily halt or modify the study based on the data monitoring committee (DMC) recommendation.

8.7 Investigational Product(s)

8.7.1 Packaging, Labeling, and Storage

8.7.1.1 rVWF (Recombinant von Willebrand Factor)

rVWF will be packaged in boxes with 2 glass vials, one containing the lyophilized rVWF, and the second vial containing the diluent. Further details are provided in the IB and Pharmacy Manual. The rVWF label will include, at a minimum, the actual VWF:RCo potency and the date of expiration.

rVWF should be refrigerated (2-8°C [36-46°F]) in lyophilized form. Deviations from the storage condition have to be communicated and followed up with the sponsor. Inadequately stored product will have to be placed in quarantine and may only be used after written investigational product administration authorization by the sponsor. After removal of the product from the refrigerator the product must not be returned to the refrigerator and has to be used immediately. rVWF must not be used beyond the expiration date printed on the vial. Avoid freezing at all times.

8.7.1.2 rFVIII (Recombinant Factor VIII /ADVATE)

ADVATE will be packaged in boxes with 2 glass vials, one containing the lyophilized rFVIII, and the second vial containing the diluent. Further details are provided in the IB and Pharmacy Manual. The ADVATE label will include, at a minimum, the actual FVIII:C potency and the date of expiration.

ADVATE should be refrigerated (2-8°C [36-46°F]) in powder form and should not be used beyond the expiration date printed on the vial. Deviations from the storage condition have to be communicated and followed up with the sponsor. Inadequately stored product will have to be placed in quarantine and may only be used after written investigational product administration authorization by the sponsor. After removal of the product from the refrigerator the product must not be returned to the refrigerator and has to be used immediately. Avoid freezing at all times.

8.7.2 Reconstitution

The reconstitution procedures for both rVWF and ADVATE products are detailed in the Pharmacy Manual.

8.7.3 Administration

Following reconstitution, rVWF and ADVATE (in case of bleeding episode treatment) should be administered to study subjects at room temperature and within 3 hours of reconstitution. The reconstituted rVWF and ADVATE, should be inspected for

particulate matter and discoloration prior to administration, whenever the solution and container permit. The solution should be clear and colorless in appearance. If not, do not administer the product. Plastic syringes provided by the sponsor must be used since coagulation factors tend to stick to the surface of glass syringes.

Investigational product infusions should be given at a rate which should not exceed 4 mL/minute. The investigator/ subject shall ensure that no visible residual volume remains in the syringe(s) and that the complete content is administered. Upon completion of the infusion, the butterfly catheter should be flushed with at least 2 mL of saline solution. In case of a (central) venous access device, the flush should be with at least 10 mL of saline solution. The IP infusions should be administered over a duration of 2 to 15 minutes, depending on the volume.

Only the actual potencies of rVWF and ADVATE as stated on the vial labels and described in the Pharmacy Manual should be used. A variation of up to 10% of the intended dose for prophylactic infusions and of the intended dose for treatment of bleeding episodes is permissible and the exact dose should be recorded on the Case Report Form (CRF).

At study visits where recovery analysis is being done, vials with the same lot numbers should be used throughout the PK IP infusion per subject.

For treatment of bleeding episodes there are 2 options for the preparation of rVWF and ADVATE for infusion if needed.

Preferably sequential administration will be done: separate syringes of the appropriate dose of rVWF and ADVATE will be prepared for sequential infusion. rVWF should be infused first sequentially followed preferably within 10 minutes by infusion of ADVATE. Only the actual potencies of rVWF and ADVATE as stated on the vial labels and described in the Pharmacy Manual should be used.

Alternatively, premixed solutions can be administered: rVWF and ADVATE will be an i.v. admixture in a single syringe to achieve the appropriate dose. The contents of each vial of rVWF or ADVATE can be drawn into 1 syringe by using a separate unused reconstitution device as described in the Pharmacy Manual.

The final dose of rVWF:ADVATE should be at a ratio of 1.3:1 ± 0.2.

8.7.4 Description of Treatment

8.7.4.1 Baseline Visit (PK-Assessment Treatment)

The first IP infusion for PK assessment should be within 42 days after the completion of screening procedures and confirmation of eligibility.

At the baseline visit the subjects will receive a dose of 50 ± 5 IU/kg rVWF:RCo for PK assessment. Blood samples will be drawn within 30 minutes pre-infusion, and at 7 time points post-infusion (30 ± 5 minutes, 60 ± 5 minutes, 6 ± 1 hours, 12 ± 1 hours, 24 ± 2 hours, 48 ± 2 hours, 72 ± 2 hours).

Subjects previously enrolled in rVWF studies **070701** or **071001** and having previously undergone PK assessments in these studies are required to repeat the PK assessment due to different dose and time points used in these former studies (see Section 12.9.1 and Section 20.3). A washout period of at least 5 days is required prior to infusion of rVWF for PK assessment for subjects previously treated with rVWF.

Subjects who participated and had a major procedure performed in the surgery study **071101** will not need an additional PK assessment. Identical PK dose and time points are used for both studies **071101** and **071301**. Subjects who participated and had a minor procedure performed in the surgery study **071101** will need a PK assessment.

8.7.4.2 Prophylaxis Initiation Treatment

The prophylaxis initiation treatment visit will coincide with the 72 ± 2 h PK assessment. At this visit subjects will receive their prophylaxis initiation dose of 50 ± 10 IU/kg rVWF:RCo after the blood draw for the 72 ± 2 hours post-infusion PK assessment. If subjects do not need an additional PK assessment (e.g., subject has participated in the surgery study **071101** and had a major procedure performed), subjects must receive the IP for prophylaxis initiation treatment within 42 days after screening and confirmation of eligibility. The exact standard prophylaxis dose may range between 40 and 60 IU/kg based on:

- available historical PK data
- type and severity of bleeding episodes the subject has experienced in the past and
- monitoring of appropriate clinical and laboratory measures

Dose adjustments during the continued prophylactic treatment are described in Section 8.7.4.3.

The subject will be trained on IP reconstitution and administration and may then qualify for home treatment (see Section 8.7.4.3.2). Refer to Table 5 for study procedures and Table 6 for clinical laboratory assessments.

8.7.4.3 Prophylaxis Treatment

The standard prophylactic dose is 50 ± 10 IU/kg rVWF:RCo. All subjects will initially receive BAX111 (rVWF) twice per week (Table 1, Schedule A). Examples of all dosing schedules are provided in Table 1.

Table 1
rVWF Dosing Schedule Examples: Schedules, A, B, and C

Example	M	T	W	Th	F	Sat	Sun	M	T	W	Th	F	Sat	Sun
Schedule A	X			X				X			X			
Schedule B	X		X			X		X		X			X	

Dose and frequency adjustments will be agreed with the sponsor in advance unless it constitutes an urgent safety measure. Dose adjustments to higher doses (not exceeding the upper dose limit of 80 IU/kg rVWF:RCo) and adjustments to frequency will only be allowed in cases of persisting high bleeding rates due to insufficient therapeutic response.

8.7.4.3.1 Treatment Escalation

Criteria for dose and frequency escalation are specific to each bleeding indication (Table 2) but, overall, involve 1 significant breakthrough bleeding episode despite compliant prophylaxis. Subjects entering the study will begin prophylaxis treatment according to Schedule A (Table 1) and will remain at this dose and frequency until meeting the criteria for escalation to the next higher schedule: for example, from 2 infusions of 50 ± 10 IU VWF:RCo/kg/week to 3 infusions of 50 ± 10 IU VWF:RCo/kg/week (Schedule B) to achieve adequate prophylaxis.

Table 2
Criteria for Escalation Specific to Each Bleeding Indication

	Schedule A	Schedule B
Joint bleeding	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a spontaneous joint bleeding episode occurs while on this regimen, the subject will escalate to Schedule B following its resolution	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
GI bleeding	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a severe GI bleeding episode occurs while on this regimen, the subject will escalate to Schedule B following its resolution	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Menorrhagia	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) on days 1 and 2 of menses for 2 cycles. Menstrual flow will be monitored by the PBAC score. If the average pictorial chart score is > 185, then the subject will escalate to Schedule B	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) on days 1, 2, and 3 of menses. Menstrual flow will be monitored by the PBAC score.
Epistaxis	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. The subject will escalate to Schedule B in the event of 1 occurrence of breakthrough bleeding requiring intervention such as iron replacement therapy, transfusion, packing, hospitalization; or 2 bleeding events that require treatment with factor replacement	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Oral and Other Mucosa	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. The subject will escalate to Schedule B in the event of 1 occurrence of breakthrough bleeding requiring intervention such as iron replacement therapy, transfusion, packing, hospitalization; or 2 bleeding events that require treatment with factor replacement.	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Muscle and Soft Tissue	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a spontaneous bleeding episode occurs while on this schedule, the subject will escalate to Schedule B following its resolution.	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.

Abbreviations: GI: gastrointestinal; PBAC: Pictorial Blood Assessment Chart.

Dose and frequency reduction will only be allowed in case plasma VWF or FVIII levels are exceeding the recommended ranges.

If a subject does not adequately respond to rVWF therapy, he/she will be evaluated for the presence of neutralizing and total binding anti-VWF antibodies (see Section 12.9.3.2).

If a subject experiences a bleed while receiving rVWF three times per week, the investigator should treat the bleed with rVWF at doses up to 80 IU VWF:RCo/kg at a frequency determined by the investigator until the bleed resolves. Upon resolution of the bleeding event, the subject will return to their assigned prophylaxis regimen.

It is essential for the success of this study that the subjects adhere to treatment regimens. Therefore, procedures for monitoring subject's compliance are implemented (see Section 10.7).

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. For example, a subject routinely infuses IP on Monday and Thursday, he/she misses the Monday time point and therefore may infuse the IP on the next day (Tuesday) and thereafter proceed with infusing the IP on Thursday (considering a minimum 12 hours between the infusions) and return to the initial schedule.

If more than 30% of infusions of IP are missed within the visit interval of 3 months the subject will be discontinued from the study (see Section 9.4).

8.7.4.3.2 General Instructions for Home Treatment for Prophylaxis

At the discretion of the investigator, a subject may be considered suitable for home treatment only after the subject has received at least 1 infusion of IP in the clinic, either during planned IP exposure (PK or prophylaxis) or during the treatment of bleeding episodes, and meets the following additional criteria:

1. Fully understands the concept of a clinical study and related documentation (documented training of at least 30 minutes),
2. Has a history of previous experience with home treatment including self-administration and treatment with VWF containing concentrates,
3. Has adequate time for initial training of the study drug preparation (preparation, mixing and infusion of the IP(s) (documented training of at least 30 minutes).

In the event a healthcare professional is required to administer IP, he/she must be trained and qualified by the sponsor on the above procedures prior to the decision for home treatment. A Subject Guideline detailing all instructions and information listed above will be provided to each subject.

8.7.4.4 Treatment of Bleeding Episodes

8.7.4.4.1 General Instructions for Home Treatment of Bleeding Episodes

If a subject experiences a bleeding episode, he/she should contact the study site immediately and the site investigator should provide instructions on the treatment regimen. If the subject initiates the treatment at home, he/she should at least follow up with the study site if a visit is needed as per the standard of care at the center.

In the event a healthcare professional is required to administer treatment at the subject's home, he/she must be trained and qualified by the site investigator on the above procedures prior to the decision for home treatment. Once a subject has received 1 infusion of rVWF in the clinic (either during planned IP exposure or during the treatment of a bleeding episode) and meets the criteria for home treatment, the treatment of bleeding episodes with IP can be conducted at home (see Section 8.7.4.3.2).

If a subject is not qualified for home treatment, rVWF infusions must be administered at the study site.

If a subject experiences a bleeding episode that requires treatment between the screening and the prophylaxis initiation visit, the subject will be treated with IP (rVWF with or without ADVATE). Treatment with IP must occur at the study site unless the subject has previously qualified for home treatment with rVWF. If rVWF treatment is not feasible, the subject may use his/her standard of care, such as commercial pdVWF/FVIII products. In any case a washout period of at least 5 days is required prior to rVWF PK infusion at the PK assessment visit.

If a subject experiences a bleeding episode requiring treatment during the PK assessment, rVWF will be used to treat the bleed. Blood draws for PK assessment will be stopped and the PK assessments will be repeated once the bleed has resolved and the subject is free of any symptoms related with the bleeding episode. Dose and frequency of rVWF infusions or any other replacement therapy to stop the bleed should be recorded in the e-CRF.

8.7.4.4.2 Dosing Recommendations for Treatment of Bleeding Episodes

If an acute bleeding episode occurs, the subject will be treated with rVWF with or without ADVATE. In general initially, an infusion of rVWF: ADVATE at an rVWF: ADVATE ratio of 1.3:1± 0.2 will be administered. Subsequent infusions may either use rVWF alone or with ADVATE, based on FVIII levels, if available.

If FVIII levels are not available, dosing is at the discretion of the investigator based upon the individual subject's PK data. Using ADVATE in addition to rVWF in subsequent

doses carries the risk of an excessive rise in FVIII:C. Therefore, reduced doses of ADVATE and/or prolongation of the dose interval should be considered.

In general the aim of the initial dose should be full replacement of VWF with VWF:RCo levels of >0.6 IU/ml (60%) and FVIII:C of >0.4 IU/mL (40%). In major bleeding episodes, subsequent doses should keep the trough level of VWF:RCo >50% for 3 days and then as deemed necessary by the investigator for subsequent days. In moderate bleeding episodes, the dose and trough level may be reduced to >30% for as long as deemed necessary by the investigator. Treatment for minor bleeding episodes will generally consist of only 1 or 2 doses of rVWF IP.

If the VWF:RCo level is above 150%, a planned treatment should be delayed by at least 12 hours; if the VWF:RCo level is above 200%, a planned treatment should be delayed by at least 24 hours. In either case, a lower subsequent dose (e.g., 20 IU/kg VWF:RCo) may be appropriate.

Dosing recommendations are listed in Table 3.

Dosage must be individualized based on the subject's weight, VWD type, and the severity of the bleeding episode, as well as on monitoring of appropriate clinical and laboratory measures. In the phase 1 study **070701**, 1.0 IU/kg VWF:RCo raised the circulating level of VWF:RCo by 0.017 IU/mL (1.7 %). In the same study, the observed mean half-life for rVWF was 19.3 hours, with a standard deviation of 10.9 hours.

Table 3
rVWF:RCo Dosing Recommendations for the Treatment of Bleeding Episodes Due to VWD

Classification of VWD	Hemorrhage	Dosage (IU VWF:RCo/kg Body Weight)
Type 1 • Severe (Baseline VWF:RCo activity typically <20%)	Minor (e.g., epistaxis, oral bleeding, menorrhagia[a])	40 to 50 IU/kg (1 or 2 doses)
	Major (e.g., severe or refractory epistaxis, menorrhagia*, GI bleeding, CNS trauma, hemarthrosis, or traumatic hemorrhage)	Initial dose 50 to 75 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment
Type 2 (all variants) and Type 3	Minor (clinical indications above)	40 to 50 IU/kg (1 or 2 doses)
	Major (clinical indications above)	Initial dose of 60 to 80 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment

[a] Menorrhagia is defined as excessive bleeding during menstruation. A diagnosis of menorrhagia will be defined by a prospectively completed Pictorial Blood Assessment Chart (PBAC) score >185 and normal cervical cytology or requiring use of a VWF-containing concentrate for treatment of excessive menstrual bleeding for at least one menstrual cycle during the prior year.

Variances of up to 10% in dosing are permissible during treatment of bleeding episodes, but rounding to the nearest vial size should be avoided.

Subjects with non-neutralizing binding anti-VWF antibodies should initially be treated with a dose known to be efficacious based on the subject's medical treatment history which may differ from the recommendations provided in Table 3. Subjects should be monitored for lack of efficacy as well as for FVIII (mandatory), VWF:RCo (mandatory), and VWF:Ag (optional where testing is not available) levels after 3 to 6 hours. Re-dosing with rVWF in combination with ADVATE using the same (initial) dose and adaptation of the dosing frequency should be considered until cessation of the bleed, if the FVIII and/or VWF:RCo levels drop below 30%-50% depending on bleeding severity.

The number of subsequent infusions and the dosage levels prescribed will be determined by the investigator on the basis of the clinical severity, response to current therapy, available laboratory data, and the subject's historical treatment for similar bleeding episodes.

8.7.5 Investigational Product Accountability

The investigator will ensure that the IP(s) is stored as specified in the Pharmacy Manual and that the storage area is secured, with access limited to authorized study personnel.

The investigator will maintain records that the IP(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. The IP(s) must be dispensed only at the study site or other suitable location (e.g., infusion center; home, as applicable per study design), as specified in the protocol (see Section 10). Records will be maintained that includes the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

8.8 Source Data

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

No data will be entered directly onto the CRF.

For additional information on study documentation and CRFs refer to Section 17.2. The use of subject diaries is described in Section 10.5.

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding
    a. Type 1 (VWF:RCo <20 IU/dL) or,

b. Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2M or,

c. Type 3 (VWF:Ag ≤3 IU/dL).

2. Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.
3. Subject currently receiving on-demand treatment for whom prophylactic treatment is recommended according to standard of care at the center.
4. Has ≥3 documented spontaneous bleeds requiring VWF treatment during the past 12 months
5. Availability of records to reliably evaluate type, frequency and treatment of bleeding episodes during 12 months of on-demand treatment prior to enrollment.
6. Subject is ≥18 years old at the time of screening and has a body mass index ≥15 but <40 kg/m^2.
7. If female of childbearing potential, subject presents with a negative blood/urine pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.[i]
8. Subject is willing and able to comply with the requirements of the protocol.

9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

1. The subject has been diagnosed with Type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD (eg qualitative and quantitative platelet disorders or elevated PT/INR >1.4).
2. The subject has received prophylaxis treatment in the 12 months prior to screening (including those who received treatment once a month for menorrhagia but were not treated for any other bleeds).
3. The subject is currently receiving prophylaxis treatment.
4. The subject has a history or presence of a VWF inhibitor at screening.
5. The subject has a history or presence of a FVIII inhibitor with a titer ≥0.4 BU (by Nijmegen modified Bethesda assay) or ≥0.6 BU (by Bethesda assay).

[i] Refer to Section 20.4 for a list of adequate contraceptive methods for females of childbearing potential.

6. The subject has a known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins.
7. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
8. The subject has a medical history of a thromboembolic event.
9. The subject is HIV positive with an absolute Helper T cell (CD4) count $<200/mm^3$.
10. The subject has been diagnosed with significant liver disease as evidenced by any of the following: serum ALT 5 times the ULN; hypoalbuminemia; portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).
11. The subject has been diagnosed with renal disease, with a serum creatinine level ≥2.5 mg/dL.
12. The subject has a platelet count <100,000/mL at screening.
13. The subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to signing the informed consent.
14. The subject is pregnant or lactating at the time of enrollment.
15. Patient has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
16. The subject has participated in another clinical study involving another IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
17. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
18. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
19. The subject has a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
20. The subject is in prison or compulsory detention by regulatory and/or juridical order.

21. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.

9.3 Delay Criteria

1. If the subject has an acute bleeding episode or presents with an acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) the screening visit will be postponed until the subject has recovered.

9.4 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (i.e., reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the termination visit (including cases of withdraw or discontinuation) are described in Section 10.6 and Section 20.2.

Discontinuation (i.e., complete withdrawal from study participation) may be due to dropout (i.e., active discontinuation by subject) or loss to follow-up (i.e., discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also will be withdrawn from treatment or discontinued from further study participation for the following reasons:

1. The subject is scheduled for an extended treatment period >3 months with non-topical immunomodulating drugs other than anti-retroviral chemotherapy (e.g., α-interferon, corticosteroid agents [equivalent to hydrocortisone greater than 10 mg/day]) during the course of the study
2. Subjects with chronic hepatitis B or C develop ALT/AST levels exceeding 5 times the ULN for >1 month
3. Subjects who experience severe hypersensitivity reactions, e.g., anaphylaxis upon exposure to rVWF
4. Subjects who develop a neutralizing inhibitor to rVWF and/or ADVATE (biological assays)
5. Subjects who demonstrate clinical signs of thromboembolic events

6. The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through completion of the pregnancy and up to 1 year post delivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome.
7. The subject begins lactating. IP exposure will be discontinued. The investigator will record a narrative description of the course of the baby's development.
8. The subject is not compliant with the prophylactic treatment regimen and does not adhere to the frequency of IP administration. Once >30% of infusions are missed within a visit interval (3 months), the subject will be discontinued from further participation in the study.

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient who provides informed consent (i.e., signs and dates the informed consent form) is considered a subject in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (e.g., 090701) to be provided by the sponsor, 2- or 3-digit number study site number (e.g., 02) to be provided by the sponsor, and 3- or 4-digit subject number (e.g., 0003) reflecting the order of enrollment (i.e., signing the informed consent form). For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 090701-020003. All study documents (e.g., CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The study site is responsible for maintaining a screening log that includes all subjects who provided informed consent. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

The overall study design is illustrated in the Figure 1. Details on the procedures to be performed at each study visit, including screening, are provided in Supplement 20.2

Schedule of Study Procedures and Assessments and Supplement 20.3 Clinical Laboratory Assessments.

10.3.1 Screening Visit

Written informed consent must be obtained from each subject before any study related procedures are performed. To initiate screening procedures, at least 72 hours must have elapsed since the last VWF administration and the subject must not be actively bleeding at the time of screening. Multimer analysis and VWD gene mutation analysis should be performed at screening if not available in the subject's medical history. The screening visit will be delayed if the subjects presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like symptoms, inflammatory diseases) until the event has resolved. All screening procedures and confirmation of eligibility shall take place within 42 days prior to the first infusion of IP for PK assessments. If the IP is not infused within 42 days, all screening assessments except blood group, human leucocyte antigen (HLA), genetics, multimeric pattern and [redacted], must be repeated to reconfirm eligibility. Refer to Supplement 20.2 and Supplement 20.3. Upon completion of screening procedures, subject eligibility will be confirmed by the sponsor on a subject eligibility form before additional study procedures are undertaken. The subject will maintain a diary that will include infusion logs (see Section 10.5). The allocation of IP will be initiated after the subject has qualified for home treatment (see Section 8.7.4.3.2).

In the event of a subject experiencing a bleeding episode that requires treatment between the screening visit and the baseline visit (PK assessment visit), the subject will be treated with rVWF. If rVWF is not available for any reason, e.g., subject not yet trained on IP administration, study site visit for IP administration not feasible, etc., the subject may use his/her standard of care, such as commercial pdVWF/FVIII products.

10.3.2 Baseline Visit - PK-Assessment Visit

After screening and confirmation of eligibility each subject will undergo a PK assessment. Subjects who participated in the surgery study **071101** will not need to undergo a PK baseline assessment again if they had a major procedure performed, provided valid PK data from **071101** is available. These subjects may proceed directly with the prophylaxis initiation visit (refer to Section 10.3.3). All subjects will receive a dose of 50 ± 5 IU/kg rVWF:RCo to determine VWF and FVIII levels. Blood samples will be drawn within 30 minutes pre-infusion, and at 7 time points post-infusion (30 ± 5 minutes, 60 ± 5 minutes, 6 ± 1 hours, 12 ± 1 hours, 24 ± 2 hours, 48 ± 2 hours, 72 ± 2 hours). See Section 20.2 and Section 20.3. IP infusion vials from the same lot number should be used for all PK-assessments per subject. Samples for measurement of

FVIII and VWF activity taken through to 6 hours post-infusion will be obtained from an extremity different from that used for the infusion of IP. Where needed, the phlebotomy site will be kept patent via an infusion of normal saline. In this event, at least 5 mL of blood will be collected and discarded before collection of the next test sample into a fresh syringe.

If the subject has a central venous catheter, the central line should be used to administer the infusion and a peripheral venipuncture should be used to collect the blood samples. In the event that a blood sample must be drawn through the central line used for administration of IP, the line must first be flushed with at least 10 mL normal saline or other suitable catheter flush solution that does not contain anticoagulant. At least 5 mL of whole blood must be collected and discarded prior to obtaining the sample.

If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.7.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment.

10.3.3 Prophylaxis Initiation Visit

After the blood sample for the 72 hour PK assessment is drawn the subject will receive the first rVWF prophylactic dose of 50 ± 10 IU/kg rVWF: RCo. Details on dose are provided in Section 8.7.4.3.

If a subject did not undergo PK assessment (for example the subject has participated in the surgery study **071101** and has undergone PK in Study **071101** and had a major procedure performed, refer to Section 8.7.4.2), procedures and assessments at this visit include: adverse events, bleeding episodes, medications taken, non-drug therapies and laboratory assessment. Independent of previous PK assessment visits, within 2 hours prior the IP infusion, a physical examination will be performed. Vital signs will be assessed within 30 minutes prior to IP rVWF infusion and 30 minutes ± 15 minutes after IP infusion. For subjects with a previous PK assessment in the course of the surgery study, incremental recovery (IR) will be determined based on VWF: RCo activity assessed prior and after IP infusion. Further details are provided in Supplement 20.2 and Supplement 20.3.

10.3.4 Treatment of Bleeding Episodes

Treatment of bleeding episodes is described in detail in Section 8.7.4.4.

10.3.5 Follow-Up Visits (1 Month ± 1 Week, 2 Months ± 1 Week, 3 Months ± 2 Weeks, 6 Months ± 2 Weeks, 9 Months ± 2 Weeks)

Visits will be performed after the prophylaxis initiation visit at 1 month ± 1 week, 2 months ± 1 week, and 3 months ± 2 weeks and thereafter every three months ± 2 weeks. Additional visits may occur if clinically indicated (see Section 10.3.6).

When possible, site visits should be scheduled on days when the subject is expected to infuse BAX111. Within 2 hours prior to the rVWF IP infusion, a physical examination will be performed. Vital signs will be assessed within 30 minutes prior to IP infusion and 30 minutes ± 15 minutes after IP infusion. Incremental recovery (IR) will be determined at each follow-up visit based on VWF:RCo activity assessed prior to and after IP infusion.

The blood sample for IR analysis will be drawn within 30 minutes prior to IP infusion and 30 minutes ± 5 minutes after IP infusion. rVWF will be infused at the regular prophylactic dose, i.e., 50 ± 10 IU/kg rVWF:RCo. For each subject's recovery analysis IP infusion, vials from the same lot number should be used.

Testing for VWF:RCo VWF:CB, rVWF:Ag, INNOVANCE VWF:Ac (exploratory) and FVIII:C level will be performed using the blood sample obtained before and after IP infusion.

The blood sample prior to IP infusion will also be used for the assessment of neutralizing and binding antibodies, clinical chemistry and hematology. A washout period of at least 72 hours after the last infusion applies before the blood draw for the immunogenicity assays. Bleeding episodes and the hemostatic efficacy will be evaluated based on the review of the patient diary. See Section 20.2 and Section 20.3. The evaluation of IP consumption and treatment compliance will be performed based on subject's diary entries. If a subject is not compliant with the prophylactic treatment regimen and does not adhere to the required frequency of administration of IP infusions (>30% of infusions were missed within a visit interval [3 months]) the subject will be withdrawn from the study.

At the 6 months ± 2 week visit an electrocardiogram (ECG) will be performed and [redacted] data will be collected.

For the hemostatic efficacy assessment the following information will be recorded by the subject in the patient diary: bleeding location, type, severity, onset and resolution date and time, infusion date and time, clinical efficacy according to the rating scale. If at any

time during the study a subject's bleeding episode does not adequately respond to rVWF therapy, he/she will be evaluated for the presence of neutralizing and total binding antibodies. Refer to Section 12.9.3.2.

Further guidance on completing the subject's diary will be provided to the subjects during training for home treatment (see Section 8.7.4.3.2).

10.3.6 Unscheduled Visits

For any unscheduled visit (except for collection of IP) a clinical assessment will be performed as per the scheduled follow-up visits with the exception of [redacted], ECG, and IR determination (refer to Supplement 20.2 and Supplement 20.3).

Subjects who have more than one bleeding episode in 3 months, or an increased frequency of bleeding, should go to the study site for an unscheduled visit.

Follow-up visits after the subject has experienced a bleed may be requested by the investigator. Additional assessments may be required which are at the discretion of the investigator.

10.3.7 Study Termination Visit (12 Months ± 2 Weeks)

At the 12 month ± 2 week visit, a full PK analysis, as per the baseline PK assessment, will be performed. Blood samples will be drawn within 30 minutes pre-infusion, and at 7 time points post-infusion (30 ± 5 minutes, 60 ± 5 minutes, 6 ± 1 hours, 12 ± 1 hours, 24 ± 2 hours, 48 ± 2 hours, 72 ± 2 hours). If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.7.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment.

The following parameters will be used as part of the PK assessment:

- Incremental recovery of VWF:RCo, VWF:Ag, VWF:CB, and INNOVANCE VWF Ac (exploratory assay)
- AUC/dose, area under moment curve (AUMC/dose, clearance (CL), Volume of distribution at steady state (V_{ss}), mean residence time (MRT), of VWF:RCo ,VWF:Ag, VWF:CB, and INNOVANCE VWF Ac (exploratory assay)
- Half-life of VWF:RCo, VWF:Ag, VWF:CB, and INNOVANCE VWF Ac (exploratory assay)

- Time course of the FVIII:C levels
- VWF collagen binding (VWF:CB) levels

Refer to Supplement 20.2 and Supplement 20.3 for the other assessments to be performed at the PK assessment and study completion visits.

A washout period of at least 72 hours is required between the PK infusion and the study termination visit (at the time of the 72 hour postinfusion PK assessment).
Refer to Supplement 20.2 and Supplement 20.3 for the list of assessments to be performed at the termination visit.

Subjects will be offered the option to continue to receive BAX111 in a long-term continuation study.

10.4 Medications and Non-Drug Therapies

The following medications and non-drug therapies are **not** permitted within 30 days before study entry and during the course of the study:

Medications:

- 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) and an extended treatment period >3 months.
- Another investigational and/or interventional study drug (except rVWF and FVIII administered under the surgery protocol).

A subject who has taken any of these medications or received any of these non-drug therapies during the study will be withdrawn from the study.

The following medications are permitted during the course of the study:

- Antifibrinolytics (e.g., tranexamic acid, ε-amino caproic acid) or topical hemostats as needed, according to each institution's standard of care
- Emergent use of a VWF concentrate other than rVWF may be permissible under certain circumstances (see Section 8.7.4.4.1)

Details of all adjunctive hemostatic medication used, including dose and reason for use, will be recorded in the electronic Case Report Form (eCRF).

10.5 Subject Diary

1. An electronic subject diary will be provided to each subject at the baseline visit to record the following information:
    - IP infusions to include date, start and stop times of the infusion, number of vials utilized, and infusion volume for prophylactic treatment or treatment of spontaneous and traumatic bleeding episodes
2. Details of bleeding episodes (site and type of bleeding) and response to treatment as described in Section 8.7.4.4
3. Subjective hemostatic efficacy assessments.

Subjects and/or their legally authorized representatives will be trained on use of the diary. The diary will be provided in electronic format and remain with the subject for the duration of the study. The investigator will review the diary for completeness and request missing information periodically and in a timely manner.

Infusions performed at the study site will be recorded in the site's source documents and not in the patient diary.

Subject entries in the diary will serve as source records. During study participation the investigator has access to the database holding the subject diary data. After study closure, the investigator will receive the diary records for their subjects, including audit trail records, in PDF format. The data will be transmitted to the CRF by a validated transfer.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have completed all study procedures according with the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, AE (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, e.g., technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the study termination visit. If the termination visit is done as an additional, unscheduled visit, the assessment

results shall be recorded with the termination visit. If a subject terminates participation in the study and does not return for termination visit, his/her last recorded assessments shall remain with the last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.2 Schedule of Study Procedures and Assessments and Supplement 20.3 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

10.7 Procedures for Monitoring Subject Compliance

Subject compliance with the procedures of this study (treatment regimens and study visits) will be monitored by the investigator or/a licensed healthcare professional at the study site.

During the regular scheduled follow-up visits a direct review of the subject's source data (e-diaries) will be performed at the sites and evaluated against the protocol requirements. In addition drug accountability will be evaluated at each follow-up study visit and the study termination visit by comparing the infusions recorded in the subject diary with empty vials returned by each subject to the study site, and the study site's dispensing record. Protocol deviations will be noted in the final report.

11. ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

11.1 Assessment of Spontaneous Bleeding Episodes/Annualized Bleed Rate

The annualized bleed rate (ABR) will be assessed based upon each individual spontaneous bleed, requiring coagulation factor replacement therapy, i.e., rVWF treatment. The following details on bleeding episodes will be recorded by the subject in the electronic diary (for home treatment), the subject's healthcare provider in the site's source documents (for treatments away from the primary investigative site), or by authorized, qualified personnel at the participating site in the subject's medical records (for hospital-based treatment):

- Location of bleed; i.e., joint, menorrhagia, epistaxis, gastrointestinal, soft tissue, muscle, body cavity, intracranial, etc.
- Type of bleed; i.e., spontaneous, traumatic, unknown
- Severity of bleed; i.e., minor, moderate, and major (see Table 3)
- Date and time of onset of bleed
- Date and time of each infusion of rVWF or rVWF-ADVATE used to treat a bleeding episode
- Date and time of resolution of the bleeding episode

Study site personnel are qualified after they have undergone training during the qualification of the site.

All types of bleeds, including traumatic bleeds, will be recorded. Bleeding episodes should be organized by where they occur in addition to whether they occurred spontaneously or due to a traumatic event.

Bleeds occurring at the same anatomical location (e.g., right knee) with the same etiology (i.e., spontaneous versus injury) within 24 hours after onset of the first bleed will be considered a single bleed. Bleeding occurring at multiple locations related to the same injury (e.g., knee and ankle bleeds following a fall) will be counted as a single bleeding episode.

All efforts should be made to use rVWF for treatment of bleeding episodes. If needed, the use of a VWF concentrate other than IP for the treatment of bleeding episodes will not disqualify the subject from further participation in the study.

11.2 Evaluation of ABR Before rVWF Prophylaxis and ABR Under rVWF Prophylactic Treatment

At screening, the subject's medical history will be recorded, including the number of all spontaneous and traumatic bleeding episodes within the past 12 months. The maximum interval of bleed-free periods as well as trauma induced bleeding episodes will also be recorded (prospectively and retrospectively).

11.3 Number of Infusions and Total Weight Adjusted Consumption of rVWF and ADVATE

The number of rVWF and ADVATE (in case of bleeding episode treatment) infusions will be logged in the subject diary. Based on these entries the weight adjusted consumption will be calculated per month and per year.

11.4 Assessment of Efficacy for Treatment of Bleeding Episode

Investigators will be asked to assess and record hemostatic efficacy after resolution of each bleeding episode using the 4-scale rating system outlined in Table 4.

Table 4
Efficacy Rating Scale

Rating	Efficacy Rating Criterion	
	Minor and Moderate Bleeding Events	**Major Bleeding Events**
Excellent (=1)	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF containing coagulation factor containing product required	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF containing coagulation factor containing product required
Good (=2)	1-2 infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required	< 1.5 x infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required
Moderate (=3)	3 or more infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required	≥ 1.5 x infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required
None (=4)	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF containing coagulation factor containing product required	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF containing coagulation factor containing product required

11.5 Pharmacokinetic Assessment

Details on pharmacokinetic assessments are provided in Section 12.9.1.

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

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, whether or not considered causally related to the IP.

12.1.1.1 Serious Adverse Event

An SAE is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse

- Reviewed and confirmed seroconversion for human immunodeficiency virus
  (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)
- Development of neutralizing VWF antibodies
- Development of neutralizing antibodies to FVIII (titer ≥0.4 BU [by Nijmegen- modified Bethesda assay] or ≥0.6 BU [by Bethesda assay])
- Thromboembolic events (e.g., myocardial infarction, stroke, transient ischemic attack [TIA], deep vein thrombosis [DVT] or pulmonary embolism)
- Anaphylaxis (for definition, refer to Section 12.6.2) or severe hypersensitivity reactions

Uncomplicated pregnancies, following maternal or paternal exposure to IP are not considered an (S)AE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE.

12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any suspected adverse reaction to study treatment (i.e., including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following:

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment

Once determined to meet the criteria for a SUSAR, the sponsor will ensure expedited SUSAR reporting in line with the regulatory requirements in participating countries as outlined in the Safety Management Plan.

12.1.1.3 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet the criteria of an SAE.

12.1.1.4 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (e.g., IB, package insert). "Unexpected" also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.1.1.5 Preexisting Disease

Preexisting diseases that are present before entry in to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described on the AE CRF.

12.1.2 Assessment of Adverse Events

For the purposes of this study, the following will not be considered as AEs and will not be included in the analysis of AEs.

- Bleeding episodes are part of the underlying disease and therefore are not AEs; they will be evaluated in the context of efficacy.
    - For non-serious bleeding episodes caused by an injury, the injury would not be reported as an AE, unless it resulted in a medical finding other than a bleeding episode (e.g., abrasion of skin). Therefore, any VWD-related bleeding event (e.g., epistaxis, gastrointestinal bleeding, musculo-skeletal bleeding, menorrhagia) that is non-serious will not be reported as an AE. However, the investigator may decide that the event is an AE if the event also would have occurred in a healthy individual under the same circumstances.
    - For SAEs: Bleeding events that meet seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) should be reported on the SAE eCRF or SAE Report form as an SAE.
- Seroconversion after documented HAV/HBV vaccination prior to or during the study period.

Each AE from the first IP exposure to the study completion date will be described on the AE CRF using the medical diagnosis (preferred), or, if no diagnosis could be established

at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2

For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution.

If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the protocol-specified dosage (including underdosing /overdosing [<20 IU/kg rVWF:RCo or >100 rVWF:RCo], abuse, and withdrawal, treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after administration of IP will be reported on a Pregnancy Form and followed-up at 1 year post-delivery, if feasible.

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the SAE Form within 24 hours after awareness: no additional reporting on CRFs is necessary.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, e.g., assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs

- Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).

- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of IP
  - An alternative etiology is equally or less likely compared to the potential relationship to the IP
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
    - Reappearance of a similar reaction upon re-administration (positive re-challenge)
    - Positive results in a drug sensitivity test (skin test, etc.)
    - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
  - Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within 5 days after IP infusion, the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

12.1.2.3 Safety Reporting

Adverse events/SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Table 5) and Section 12.1.2.

Adverse Events/SAEs are to be recorded on the AE page of the eCRF. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the investigational product, must be reported immediately (within 24 hours of the study center's first knowledge of the event). All SAEs must be reported via the

Electronic Data Capture (EDC) system by completing the relevant eCRF page(s) in English. For instances in which the EDC may become unavailable, SAEs must be reported using the back-up paper SAE report (SAER) form to meet the 24-hour timeline requirement (for contacts and instructions refer to the SAER form). Once the EDC becomes available, the site must enter all SAE data as reported on the back-up paper SAER form on the applicable eCRF pages.

The initial SAE information reported on the applicable eCRF pages (or back-up SAER Form, if applicable) must at least include the following:

1. Protocol Number
2. Subject identification number and demographics (gender, age at onset of event and/or date of birth)
3. Investigational product exposure
4. Medical Term for Event (Diagnosis preferably)
5. Description of the (S)AE, including:
    - Date of onset
    - (S)AE treatment (drug, dose, route of administration)
    - Causal relationship by the Investigator
    - Measures taken (i.e., action taken regarding investigational product in direct relationship to the AE)
6. Seriousness criteria (ie, death, life-threatening, or other criterion)
7. Cause of death
8. Autopsy findings (if available)
9. Name, address, fax number, email, and telephone number of the reporting Investigator (for paper SAER Forms)

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures

- Temporary or permanent halt of a given clinical trial or trials
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor.
In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committees (ECs) and relevant competent authority(s) are notified of the urgent measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (i.e., from the time of signed informed consent up to but not including the first IP exposure) will be described on the SAER. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE.** NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g. reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (e.g., potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) 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. The subject's medical history will also include documented history of on-demand treatment for the past 12 months and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 months.

All medications taken and non-drug therapies received in the 2 weeks prior to study entry and all concomitant medications and non-drug therapies during study will be recorded on the CRFs.

Data on medical history, drug and non-drug therapy history of those subjects who transition from surgery rVWF study will be used from the eCRF of the main studies, will be updated, if applicable, and transcribed into the respective eCRF of the prophy study.

12.6 Physical Examinations

At screening and subsequent study visits (as described in Section 10.3), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 12.1.1.5), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.6.1 Thromboembolic Events

Thromboembolic events are considered a potential risk of rVWF treatment, hence, clinical evidence of thrombosis will be monitored during the study. In the case of clinical signs of any thromboembolic event other than superficial thrombosis, additional diagnostic procedures are required according to each institution's standard of care which may consist of, but are not limited to the following:

- For deep vein thrombosis (DVT): Magnetic Resonance Imaging (MRI), compression ultrasound or impedance plethysmography.
- For pulmonary embolism: ECG, chest radiography, perfusion/scintiscan or MRI.
- For myocardial infarction: ECG, cardiac enzymes, echocardiography
- For stroke: diffusion-weighted magnetic resonance imaging or computed tomography, ABCD scoring, carotid imaging

Results of diagnostic procedures may be forwarded to the sponsor to be reviewed by an independent external expert panel, such as the DMC, if applicable.

12.6.2 Anaphylaxis

The diagnosis of anaphylaxis is highly likely when any of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g, generalized urticaria, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
    b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a. Involvement of the skin or mucosal tissue (e.g., generalized urticaria, pruritus or flushing, swollen lips-tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

c. Reduced BP or associated symptoms (hypotonia [collapse], syncope, incontinence)

d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to a known allergen for that patient (minutes to several hours):

   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP

   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP

If a subject develops anaphylaxis in the course of the clinical study this needs to be reported as SAE (Section 12.1.1.1). Additional blood draws for Anti-VWF IgE antibody testing will be drawn (Section 12.9.13).

12.7 Vital Signs

Vital signs will be assessed pre and post-infusion at each visit, if not stated otherwise:

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

Vital signs (pulse rate, respiratory rate, and blood pressure) should be recorded within 30 min before and after IP administration. The assessment of vital signs per planned study visit is outlined in Supplement 20.2.

Vital sign values are to be recorded on the physical examination eCRF. For each vital sign value, the investigator will determine whether the value is considered an AE (see definition in Section 12.1). If assessed as an AE, the medical diagnosis (preferably), symptom, or sign, will be recorded on the AE eCRF. Additional tests and other

evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE, should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.8 Electrocardiogram

A standard 12-lead ECG at rest will be performed at screening, at the 6 month follow-up visit and at the study termination visit and evaluated for medical significance by the investigator.

12.9 Clinical Laboratory Parameters

Refer to the Laboratory Manual for information on collection and processing of samples.

In general all laboratory tests will be performed at central laboratories, except the pregnancy and blood group test which will be performed at the local laboratory. In addition, relevant critical safety laboratory tests for complete blood count (CBC), serum chemistry and/or coagulation parameters such as VWF and FVIII activity may also be performed in the local laboratory to ensure that results will be available immediately to the investigator. In principle, results from the central laboratory will be used for data analysis purposes. The assays performed in the central laboratories are specified in the Laboratory Manual. The investigator will supply the sponsor with a list of the normal ranges and units of measurement for the laboratory variables to be determined at the site. Laboratory values such as antibodies to other proteins are not required immediately and will be assessed later during the course of the study.

Abnormal laboratory values deemed clinically significant by the investigator are to be recorded as AEs (see Section 12.1.2).

12.9.1 rVWF and Endogenous FVIII Pharmacokinetics

PK assessments using a dose of 50 IU ± 5 IU/kg rVWF:RCo will be performed at the baseline visit. If the subject is on on-demand treatment and has received VWF replacement therapy a washout period of at least 5 days is required before the infusion of rVWF for PK assessment can be administered.

Blood samples will be drawn within 30 minutes pre-infusion, and at 7 time points post-infusion (30 ± 5 minutes, 60 ± 5 minutes, 6 ± 1 hours, 12 ± 1 hours, 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours) VWF activity will be determined using the VWF:RCo, VWF:CB and the VWF: Ag assay. The Innovance assay will be used as an exploratory assay to provide supportive data and to compare the results of this new assay with results from the established VWF:RCo assay.

Endogenous FVIII activity will be measured using the 1-stage clotting assay.

At the 12 month ± 2 week visit, a full PK analysis will also be performed. Blood samples will be drawn within 30 minutes pre-infusion, and at 7 time points post-infusion (30 ± 5 minutes, 60 ± 5 minutes, 6 ± 1 hours, 12 ± 1 hours, 24 ± 2 hours, 48 ± 2 hours, 72 ± 2 hours). If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.7.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment.

The following parameters will be used as part of the PK assessment:

- Incremental recovery of VWF:RCo, VWF:Ag, VWF:CB and INNOVANCE VWF Ac (exploratory assay)
- AUC/dose, area under moment curve (AUMC/dose, clearance (CL), Volume of distribution at steady state (V_{ss}), mean residence time (MRT), of VWF:RCo ,VWF:Ag, VWF:CB and INNOVANCE VWF Ac (exploratory assay)
- Half-life of VWF:RCo, VWF:Ag, VWF:CB and INNOVANCE VWF Ac (exploratory assay)
- Time course of the FVIII:C levels
- VWF collagen binding (VWF:CB) levels

12.9.2 Hematology and Clinical Chemistry

The hematology panel will consist of CBC [hemoglobin, hematocrit, erythrocytes (ie, red blood cell count [RBC]), and leukocytes (i.e., white blood cell count [WBC])] with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.

The clinical chemistry panel will consist of sodium (Na), potassium (K), chloride (Cl), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), bilirubin (BILI), alkaline phosphatase (AP), blood urea nitrogen (BUN), creatinine (CR), and glucose (Glu).

Blood will be obtained for assessment of hematology and clinical chemistry parameters at screening, during PK-assessment prior to rVWF IP infusion, after 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours post rVWF IP infusion, at all follow-up visits as per schedule (refer to Supplement 20.3 Clinical Laboratory Assessments), i.e., 4 weeks ± 1 week, 8 weeks ± 1 week and every 3 months ± 2 weeks, and at study completion. Hematology and clinical chemistry assessments will be performed on

Ethylenediaminetetraacetic acid (EDTA)-anticoagulated whole blood and serum, respectively, at the central laboratory.

12.9.3 Immunology

12.9.3.1 Antibodies to VWF and FVIII

All subjects will be tested for binding and neutralizing antibodies to VWF and FVIII at screening, at baseline PK assessment, at each of the scheduled follow-up visits and at the study completion visit. Testing will be done prior to IP infusion and with at least a 72 hour wash out period since the last IP infusion. If there is any suspicion of inhibitor development (e.g. excessive bleeding) binding and neutralizing antibodies to VWF and FVIII may be tested at the discretion of the investigator.

12.9.3.2 Neutralizing and Total Binding Anti-VWF Antibodies

The assays to establish the presence of neutralizing and total binding anti-VWF antibodies have been established in the absence of international standards and with only limited numbers of positive controls. Therefore, caution is advised in interpreting positive results. In particular, any clinical association, changes in the natural history of the disease, effect of therapy, etc. needs to be taken into account for final judgment. The sponsor's Medical Director should be consulted for additional advice. As part of the AE follow-up, any sample testing positive needs to be confirmed after 2-4 weeks for central laboratory testing. Only confirmed neutralizing anti -VWF antibodies are considered inhibitors (see Section 12.9.3.4). These subjects need to be closely monitored and therapy adjusted accordingly.

12.9.3.3 Binding antibodies to VWF

The presence of total binding anti-VWF antibodies will be determined by an enzyme-linked immunosorbent assay (ELISA) employing polyclonal anti-human Immunoglobulin (Ig) antibodies (IgG, IgM and IgA). For this assay (ELISA), recombinant human VWF will be coated onto a microtiter plate, then incubated with dilutions of the positive control, the negative control or test sample. Antibodies against human VWF that are present in the samples bind to the coated antigen and will be detected with a horseradish peroxidase (HRP)-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a human monoclonal antibody specific for human VWF spiked into the negative control. The negative control for this assay is pooled normal human plasma.

Plasma samples are analyzed for binding antibodies against the specific antigen in two steps. First, the sample is screened for antibodies and the titer of binding antibodies is

determined. Second, the specificity of positive antibody results is confirmed.[16]
In brief, all samples are serially diluted (initial dilution 1:20 and further diluted 1:2).

The titer endpoint, defined as the highest dilution that still gives a positive signal above cut off level, is determined in two independent duplicates. The cut off level is established based on background signal level of healthy plasma donors (n=160) and set to include 5% false positives to be as sensitive as possible (95% percentile). The ELISA assay is validated allowing an assay variability of ± 1 titer step. Therefore, differences ≤ 2 titers steps may be due to variability of the ELISA assay. Specificity has to be confirmed in a competition assay when a sample has a titer of 1:80 or higher in the screening assay. Based on the validation criteria samples tested in the screening assay at 1:20 or 1:40 cannot be confirmed in the competition assay. A positive screening value is confirmed if the difference between the titers determined for the subject sample (re-screen) and for the subject sample with pre-incubation (confirmation sample) is > 2 titer steps. Antibody titers of subject samples will only be reported as positive, if the results of the screening and confirmatory analysis fulfill these acceptance criteria. The titer to be reported is always the one determined in the original screening procedure (independent of the result of the re-screening in the confirmation procedure).

A more detailed test procedure will be supplied upon request or pro-actively if a sample tests positive. A treatment related increase of the binding anti-VWF antibodies is expected, if the titer increases by more than 2 titration steps. These subjects need to be closely monitored and therapy adjusted accordingly.

12.9.3.4 Neutralizing Antibodies to VWF

Three functional VWF assays, collagen binding (VWF:CB) assay, Ristocetin cofactor (VWF:RCo) and FVIII binding (VWF:FVIIIB), will be used to test for the presence of neutralizing anti-VWF antibodies. Neutralizing antibodies to VWF:RCo, VWF:CB and VWF:FVIIIB activities will be measured by assays based on the Bethesda assay established for quantitative analysis of FVIII inhibitors (Nijmegen modification of the Bethesda assay).[17] The amount of inhibitor is expressed as Bethesda units (BU) per mL. One BU is thereby defined as the amount of inhibitor that decreases the measured activity in the assays to 50% of that of the negative control samples. The assays were validated using human plasma samples from two type 3 VWD patients with low (1-2 BU/mL) and high (~10 BU/mL) titer inhibitors and plasma samples from non-human primates immunized with human rVWF (>100 BU/mL)

If a subject has a measurable baseline level of VWF activity in the respective assay, it is taken into account in the calculation of the residual activity. However, if baseline levels are too high (>15% VWF:RCo), inhibitors may not be reliably detected.

To exclude false positive results, the detection limit for anti-VWF inhibitors was set to 1 BU/ml for all 3 assays. The rationale for this cut-off value is the relatively high CI of the underlying assays, making determinations at the end of the evaluation range of the Bethesda reference curve uncertain.[18]

A more detailed test procedure may be requested to further characterize the anti-VWF inhibitors, if detected.

12.9.3.5 Binding Antibodies to FVIII

Binding antibodies against FVIII will be analyzed using a proprietary enzyme immunoassay. The testing strategy will be as described for binding anti-VWF antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.3.6 Neutralizing Antibodies (Inhibitors) to FVIII

Neutralizing antibodies (inhibitors) to FVIII will be assessed by the Nijmegen modification of the Bethesda assay in a central laboratory. To verify a FVIII inhibitor, additional testing (such as tests for Lupus anticoagulants) may be initiated. Positive FVIII inhibitor tests will be defined as ≥ 0.4 BU by the Nijmegen-modified Bethesda assay that is confirmed by a second test performed on an independent sample obtained 2-4 weeks following the first test. Only confirmed positive FVIII inhibitor test result will be reported as an SAE.

12.9.4 Antibodies to Other Proteins

Plasma will be assayed for the presence of antibodies against CHO protein (total Ig), murine IgG and human Furin (total Ig) using proprietary enzyme immunoassays. The testing strategy will be as described for binding anti- VWF antibodies.
Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.4.1 Anti-CHO Protein

Total Ig antibodies (IgG, IgA, IgM) against CHO protein will be analyzed. For this assay (ELISA), CHO protein derived from cultures of untransfected cells and propagated under the identical cell culture conditions used for ADVATE production will be coated onto a microtiter plate, then incubated with dilutions of the positive control, negative control or test sample. Antibodies against CHO protein that are present in the samples bind to the

coated antigen and will be detected with a horseradish peroxidase (HRP)-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a polyclonal goat anti-CHO protein antibody spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.4.2 Anti-Murine IgG

A commercially available ELISA (Medac, Hamburg, Germany) will be used to detect and to quantify IgG antibodies originating from human plasma that are directed against mouse-IgG (HAMA: human anti- mouse antibodies). Microtiter plates coated with mouse IgG will be incubated with dilutions of the standard, the positive control, the negative control or the test sample. Antibodies against mouse IgG that are present in the samples bind to the coated antigen and form a bridge to a peroxidase coupled mouse IgG antibody that will be used for detection (bridging format of the ELISA assay). The positive control for this assay will be a polyclonal goat anti-murine IgG spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.4.3 Antibodies to Human Furin

Total Ig antibodies (IgG, IgA, IgM) against human Furin will be analyzed. For this assay (ELISA), recombinant human Furin will be coated onto a microtiter plate, then incubated with dilutions of the positive control, the negative control or test sample. Antibodies against human Furin that are present in the samples bind to the coated antigen and will be detected with a horseradish peroxidase (HRP)-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a human monoclonal antibody specific for human Furin spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.5 Viral Serology

The following viral seromarkers will be assessed at screening:

- HIV: anti-HIV 1, HIV 2
- HAV: anti-HAV (IgG and immunoglobulin M [IgM])
- HBV: Hepatitis B surface antigen (HbsAg), anti-Hepatitis B (HB) core, anti-HBs
- HCV: anti-HCV ELISA
- Parvovirus B19: anti-B19V (IgG and IgM)

Virus serology will be established during the screening period. The relevant confirmatory Polymerase Chain Reaction (PCR) testing may be performed from appropriate left-over samples as needed.

12.9.6 Urinalysis (Dipstick)

The urinalysis will include assessments for erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite and pH and will be performed at the central laboratory.

12.9.7 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. The pregnancy test may need to be repeated during the course of study in countries where mandated by national law.

12.9.8 VWD Mutational Analysis, Multimer Analysis and Human Leukocyte Antigen Genotyping

A cell pellet (buffy coat and erythrocytes) will be retained at the screening visit for VWD gene mutational analysis, VWF multimer analysis and HLA genotype determination if the information is not already available in the subject's medical history. Results from multimer analysis (see Section 12.9.10.1) may contribute to VWD gene mutational analysis. The genetic testing will be done, when the subject consents to the genetic testing.

12.9.9 Blood Group Analysis

The blood group needs to be determined during the screening period. If the information is not already available in the subject's medical history, it has to be determined at the local lab.

12.9.10 Additional Laboratory Testing in Case of Thromboembolic Events

rVWF contains ultra large molecular weight (ULMW) multimers because of a lack of exposure to endogenous VWF protease (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) during the manufacturing process. In vitro and in vivo cleavage of these ultralarge molecular fractions by ADAMTS13 and generation of characteristic satellite bands has been extensively demonstrated during nonclinical and clinical development. Nevertheless, the potential elevated risk of thrombosis and/or other thromboembolic complications due to the administration of ultra large molecular VWF multimers in subjects with normal levels of

VWF cannot be completely excluded. Therefore VWF multimer analysis will not only be performed routinely at screening but in case of thromboembolic events both VWF multimer analysis as well as ADAMTS13 activity will be determined to assess any relatedness of these occurrences with IP treatment.

12.9.10.1 VWF Multimer Analysis

The VWF multimer pattern will be assessed using low-resolution sodium dodecyl sulfate (SDS)–agarose gel electrophoresis. High-resolution SDS–agarose gel electrophoresis, with agarose concentrations >1.5%, will be used to determine the satellite band structure of VWF. These analyses will employ Western blot with luminescence video imaging.

12.9.10.2 ADAMTS13 Activity

VWF73 was identified as the 73 amino acid minimal region of the VWF A2 domain required for ADAMTS13 cleavage. The cleavage of this substrate will be detected by a commercially available ELISA-based Chromogenic assay (Technoclone Austria): Cleavage of immobilized VWF73 substrate is detected by a HRP-labeled antibody directed against the cleavage site of VWF73. The amount of bound antibody, which is the function of the ADAMTS13 cleavage is detected by a chromogenic substrate.

12.9.11 Soluble P-Selectin (sP-Selectin)

sP-selectin is a cell adhesion molecule (CAM) found in granules in endothelial cells (cells lining blood vessels) and activated platelets. Data for an association between the sP-selectin concentration, thrombotic thrombocytopenic purpura (TTP) and venous thromboembolism (VTE) are limited and the predictive value has not yet established. A commercial ELISA assay will be employed as an exploratory test. sP-selectin will be determined at the Screening visit and used as indicator for an increased thrombotic risk.

12.9.12 D-Dimer

D-dimer will be used as a marker for DVT and disseminated intravascular coagulation (DIC). While a negative result practically rules out thrombosis, a positive result can indicate thrombosis but does not rule out other potential etiologies, including a recent hemorrhage. Its main use, therefore, is to exclude thromboembolic disease where the probability is low. D-Dimer will be measured at the Screening visit and used as indicator for an increased thrombotic risk.

12.9.13 Additional Laboratory Testing in Case of Severe Hypersensitivity Reactions

If a subject develops a severe hypersensitivity reaction in the course of the clinical study, additional blood draws for anti-VWF IgE antibody testing will be drawn. The presence of

anti-VWF IgE will be determined by using the ImmunoCAP®, a VWF-specific IgE blood test (Thermo Scientific). The basis of the ImmunoCAP® technology is a cellulose polymer as solid phase in a plastic capsule providing a large surface for protein binding. rVWF as antigen is covalently coupled to the cellulose polymer. Detection of specific anti-VWF IgE bound to the antigen will be accomplished by a secondary enzyme-labeled anti-human IgE antibody. Testing for binding anti-human VWF IgE antibodies will be done with 0.5 mL plasma. Antibody containing samples will be identified and quantified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.14 Exploratory Assay

The INNOVANCE VWF Ac: an assay, which will eventually replace the VWF:RCo test in the future, will be done using the same time points/blood draws including PK assessment as outlined for the VWF:RCo assessments. The VWF Ac assay is a sensitive test for direct determination of VWF activity. It employs an advanced new technology, allowing the assay to mimic the reaction in which VWF binds to glycoprotein Ib (GPIb), the major VWF receptor protein on platelets. Latex particles are coated with an antibody against GPIb, to which recombinant GPIb is added.

12.9.15 Assessment of Laboratory Values

12.9.15.1 Assessment of Abnormal Laboratory Values

For VWF and FVIII laboratory assessments no evaluation of clinical significance is necessary.

Each other laboratory value (except results to determine genetics of the underlying VWD disease and blood group) has to be assessed by the investigator and the assessment will be recorded on the eCRF. The investigator will determine for each abnormal laboratory value whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 12.1) and record the sign, symptom, or medical diagnosis on the AE CRF, is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.5), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, i.e. because it is due to a preexisting disease, due to a lab error, due to variation or due to another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

Any seroconversion result for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V) shall be re-tested.

12.10 [redacted]

12.10.1 [redacted]

12.10.2 [redacted]

[redacted]

13. STATISTICS

13.1 Sample Size and Power Calculations

The determination of the sample size for this study is not based on strict statistical considerations. The sample size of a subset of at least 15 subjects with severe VWD, 5 of whom must have Type 3 VWD, is based on the Guideline on the Clinical Investigation of Human Plasma Derived von Willebrand Factor Products (CPMP/BPWG/220/02).[1]

13.2 Datasets and Analysis Cohorts

13.2.1 Safety Analysis Set

The Safety Analysis Set will be composed of all subjects who received any amount of IP, rVWF:ADVATE or rVWF alone.

13.2.2 Full Analysis Dataset

The Full Analysis Set (FAS) will be composed of all subjects with available bleeding data gathered during prophylaxis IP treatment.

13.2.3 Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set will be composed of subjects who are at least 70% compliant regarding required prophylactic infusions. Only subjects who met all study entry criteria and who had no major protocol violations that might impact efficacy assessments will be included in the PP analysis set.

13.2.4 PK Full Analysis Set

The Pharmacokinetic Full Analysis Set (PKFAS) will be composed of all subjects who received the PK infusion and who provided acceptable data for PK analysis. Acceptable PK data will be defined in the Statistical Analysis Plan.

13.2.5 PK Per Protocol Analysis Set

The Pharmacokinetic 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 affecting the PK period of the study as defined in the detailed Statistical Analysis Plan.

13.3 Handling of Missing, Unused, and Spurious Data

13.3.1 General

Statistical techniques will not be used to identify and exclude any observations as outliers from the analyses. If data are considered spurious, e.g. for lack of biological plausibility, it will be documented to include the reason for exclusion and the analyses from which the data were excluded.

13.3.2 Other

1. Regarding missing data in PK records:
   - Body weight: If a subject's weight is missing from the PK infusion record, the subject's last recorded weight will be used to calculate the weight-adjusted dose.
   - Concentration:
   - Baseline concentration levels reported as below the limit of quantification will be considered to be 0. Missing VWF baseline concentration levels (VWF: RCo, VWF: AG or VWF: CB) for Type 3 subjects will be set to 0.
   - Time:
   - If start time of infusion is missing (but stop time is available) and actual collection time is available, then stop time of infusion will be taken for further calculation (i.e. time difference between actual end date/time of infusion and date/time blood sample drawn).
     - If actual collection date/time is missing and planned collection date/time is missing, then this PK time point will be taken out from the PK analysis (i.e. no data entry for this time point).
     - For all other scenarios, the planned collection date/time will be taken for further calculation.
2. Regarding missing data in AE records:
   - Handling of unknown causality assessment:
     - If a subject experiences an AE with a missing causality assessment, the relationship of the AE will be counted as "related."
   - Handling of unknown severity grades:
     - If a subject experiences more than one AE categorized under the same preferred term, 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.

13.4 Methods of Analysis

The study success criteria are the objectives as stated in Section 7. “Treatment success” was defined as the extent of control of bleeding episodes achieved during this study.

13.4.1 Primary Outcome Measure

The statistical analysis will provide descriptive summaries.

For the number of infusions and for the total weight adjusted consumption of rVWF and ADVATE per month and per year during on-demand treatment, summary statistics will be carried out.

For the number (proportion) of subjects with reduction of ABR relative to historic ABR as well as for the number (proportion) of subjects with 0 bleeds, proportions and corresponding 95% two-sided CIs will be performed.

The annualized rate of bleeding episodes will be calculated as (Number of bleeding episodes/observed treatment period in days) * 365.25.

The primary efficacy analysis will be based on the FAS. As a supportive analysis, the same analysis will also be carried out on the PP.

The two time periods (prior to prophylaxis treatment and while on prophylaxis) will be compared within each subject in terms of mean ABR using a generalized estimating equations model framework (with a logarithmic link function which was the default for the negative binomial distribution), accounting for the fixed effect of the two time periods. The follow-up time (in years) will be specified as an offset and an unstructured working correlation matrix will be used to account for the correlated data. Ratios between the two time period means (95% CI) will be estimated within this model by SAS procedure GENMOD.

13.4.2 Secondary Outcome Measures

13.4.2.1 Efficacy

For the number of infusions and for the total weight adjusted consumption of rVWF and ADVATE per month and per year during on-demand treatment for bleeding episodes, summary statistics will be carried out.

For the number (proportion) of subjects with reduction of ABR relative to historic ABR as well as for the number (proportion) of subjects with 0 bleeds, proportions and corresponding 95% two-sided CIs will be performed.

The cause, type, localization and severity of bleeding episodes will also be recorded and summarized. Bleeding episodes should be organized by where they occur in addition to whether they occurred spontaneously or due to a traumatic event.

The secondary efficacy analysis will be performed on the FAS only.

13.4.2.2 Efficacy of the Treatment of Bleeding Episodes

For the number of infusions of rVWF and ADVATE per bleeding episode, for the weight adjusted consumption of rVWF and ADVATE per bleeding event as well as for the overall hemostatic efficacy rating at resolution of bleed, summary statistics will be carried out.

The severity and localization of bleeding episodes will also be recorded and summarized.

The analysis will be performed on the FAS.

13.4.2.3 Pharmacokinetic Analysis

All PK analyses will use the actual sampling times, not nominal times specified in the protocol, wherever possible. Actual sampling times will be defined as time from the start of infusion to the blood sample collection time. A deviation from the protocol-specified blood sample 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 results were biologically implausible will be eliminated from the analysis.

If any concentration data are considered spurious (e.g. lack of biological plausibility), the reason for exclusion from the analysis and the analysis from which the data point was excluded will be documented.

To ensure that values at baseline (pre-infusion) are not affecting the estimation of PK parameters, post-infusion concentration data will be adjusted for baseline as follows:

$$C_{Corrected,\ t} = (1 - \frac{C_{Measured,\ pre-infusion}}{C_{Measured,\ Tmax}}) \cdot C_{Measured,\ t}$$

After adjustment of the post-infusion concentration data, any pre-infusion data will be set to 0.

$C_{Corrected}$ will be set to missing, if:

- Samples have an unknown draw time or where the concentration could not be determined, or where results were deemed to be unreliable due to analytical issues.
- Any concentration data are considered spurious (e.g. lack of biological plausibility).

Handling of concentrations that are below the quantification limit:

- Baseline concentration values reported as below the limit of quantification will be considered to be 0 ($\rightarrow C_{Corrected}$ = Concentration value)
- Post-infusion concentration values reported as below the limit of quantification or missing repeated concentration values will be set to missing ($\rightarrow C_{Corrected}$ = missing)

The area under the plasma concentration/time curve from time 0 to infinity ($AUC_{0-\infty}$) and the area under the first moment curve from time 0 to infinity ($AUMC_{0-\infty}$) will be calculated as the sum of AUC or AUMC from time 0 to the time of last quantifiable concentration plus a tail area correction calculated as C_t/λ_z and $C_t/\lambda_z(t + 1/\lambda_z)$, respectively, where C_t is the last quantifiable concentration, t is the time of last quantifiable concentration and λ_z is the terminal or disposition rate constant.

The area under the plasma concentration/time curve from time 0 to 72 hours post-infusion (AUC_{0-72h}) will be computed using the linear trapezoidal rule. For the calculation of AUC_{0-72h} the levels at 72 hours will be linearly interpolated/ extrapolated from the 2 nearest sampling time points.

Elimination phase half-life (HL) in hours will be calculated as:

$$T_{1/2} = log_e(2)/\lambda_z$$

where the elimination rate constant (λ_z) will be obtained by $\log_e$-linear fitting using least squares deviations to at least the last 3 quantifiable concentrations above pre-infusion level.

The **Mean Residence Time** (MRT) in hours will be calculated as total area under the moment curve divided by the total area under the curve:

$$MRT = \frac{AUMC_{0-\infty}[h^2 * IU/dL]}{AUC_{0-\infty}[h * IU/dL]}$$

Systemic clearance in dL/kg/h will be calculated as the dose in IU/kg divided by the total AUC:

$$CL = \frac{Dose[IU/kg]}{AUC_{0-\infty}[h * IU/dL]}$$

Apparent **steady state volume of distribution** (Vss) in dL/kg will be calculated as:

$$Vss = \frac{Dose[IU/kg] \times AUMC_{0-\infty}[h^2 * IU/dL]}{AUC^2_{0-\infty}[h^2 * IU^2/dL^2]}$$

The **maximum concentration**, C_{max}, will be calculated as the maximum concentration post-infusion.

The **time to reach the maximum concentration**, T_{max}, in hours was defined as the time to reach C_{max}.

Incremental recovery (IR) in (IU/dL)/(IU VWF:RCo/kg) will be calculated as:

$$IR = \frac{C_{max}[IU/dL] - C_{pre-infusion}[IU/dL]}{dose\ per\ kg\ body\ weight\ [IU/kg]}$$

where C_{max} and $C_{pre\text{-}infusion}$ are the unadjusted concentration values.

The PK parameters $AUC_{0\text{-}72h}$/Dose, $AUC_{0\text{-}\infty}$/Dose, $AUMC_{0\text{-}\infty}$/Dose, MRT (mean residence time), CL (clearance), IR (incremental recovery), $T_{1/2}$ (elimination phase half-life), Vss (Volume of distribution at steady state), C_{max} (maximum concentration) and T_{max} (time to reach the maximum concentration) will be summarized by mean, standard deviation and the corresponding 90% CIs, median, Q1, Q3, IQR and range.

Descriptive statistics will be used to summarize VWF:RCo levels for each nominal time point on the PK curve.

PK analysis as described above will be carried out on the PKFAS as well as on the PKPPAS.

For all subjects in the PKFAS concentration vs. time curves will be prepared.

PK parameters will be derived using non-compartmental methods in WinNonlin.

The analysis will be performed on the FAS.

13.4.2.4 Safety

AEs that occurred during or within 24 hours after first IP infusion will be presented in summary tables. Summary tables shall indicate the number of subjects who experienced adverse events. Separate tables will be carried out for temporally associated adverse events; and for temporally associated or causally related adverse events.

In addition, tables will be prepared to list each AE, the number of subjects who experienced an AE at least once, and the rate of subjects with AE(s). AEs will be grouped by system organ class. Each event will then be divided into defined severity grades (mild, moderate, severe). The tables will also divide the AEs into those considered related (a "possibly related" or a "probably related" AE will be considered as a "related AE") to the treatment and those considered unrelated (an "unlikely related" or a "not related" AE will be considered as an "unrelated" AE). These tables will also be carried out for temporally associated adverse events; and for temporally associated or causally related adverse events.

All AEs; temporally associated AEs; causally related AEs (by investigator assessment); and temporally associated or causally related AEs will also be summarized by system organ class, preferred term, including the number of AEs, the number (%) of unique subjects, the frequency category (very common: ≥10%, common: ≥1% to <10%, uncommon: ≥0.1% to <1%, rare: ≥0.01% to <0.1%, very rare: <0.01%) and the number of IP-infusions associated with an AE.

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 infusion, irrespective of being related or not related to treatment.

AEs and SAEs for each subject, including the same event on several occasions, will be listed separately, giving both MedDRA preferred term and the original verbatim term used by the investigator, system organ class, severity grade, seriousness, relation to the treatment (by investigator assessment; for SAEs this will be by investigator and sponsor assessment), onset date, and stop date.

AEs that occurred before first IP infusion will be listed separately.

Incidences of thromboembolic events and hypersensitivity reactions will be tabulated and also listed per subject. For the development of antibodies, proportions will be carried out.

The safety analyses will be based on the safety analysis set.

13.5 Exploratory Outcome Measures

[redacted]

13.6 Planned Interim Analysis of the Study

No formal interim analysis is planned for this study. However, a descriptive summary report for this study is planned after all subjects have completed at least 6 months of prophylactic treatment with rVWF.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Trial Agreement (CTA). If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the CTA.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable national and local regulatory requirements as described in the CTA. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

15.1.1 Investigator Report and Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the CTA. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the CTA. Auditing processes specific to the study will be described in the audit plan.

15.5 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor (Baxalta) will also ensure the responsible EC and relevant competent authority are notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.6 Laboratory and Reader Standardization

A central laboratory/reader will be used for all clinical assessments except for pregnancy testing and blood group test (refer to Section 12.9). Local laboratories are requested to provide their laboratory specifications of the individual tests that are also being tested locally.

16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the CTA.

16.2 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the CTA.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be

implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

16.3 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients and/or their legally authorized representative must sign an informed consent form before entering into the study according to applicable national and local regulatory requirements and ICH GCP. Before use, the informed consent form will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 16.2). The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable national and local regulatory requirements. Patients or their legally-authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent form, patients or their legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised informed consent form, which have been approved by the applicable EC and regulatory authorities, will be provided by the investigator to the subjects who consented to participate in the study

16.4 Data Monitoring Committee

This study will be monitored by Data Monitoring Committee (DMC). The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. 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 stop a trial if it finds toxicities or if treatment is proven to be not beneficial. Details will be defined in the DMC charter.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the CTA.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.8), records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, CRFs, SAERs, laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

If electronic format CRFs are provided by the sponsor, only authorized study site personnel will record or change data on the CRFs. If data is not entered on the CRFs during the study visit the data will be recorded on paper and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (e.g., ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the CTA.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the CTA.

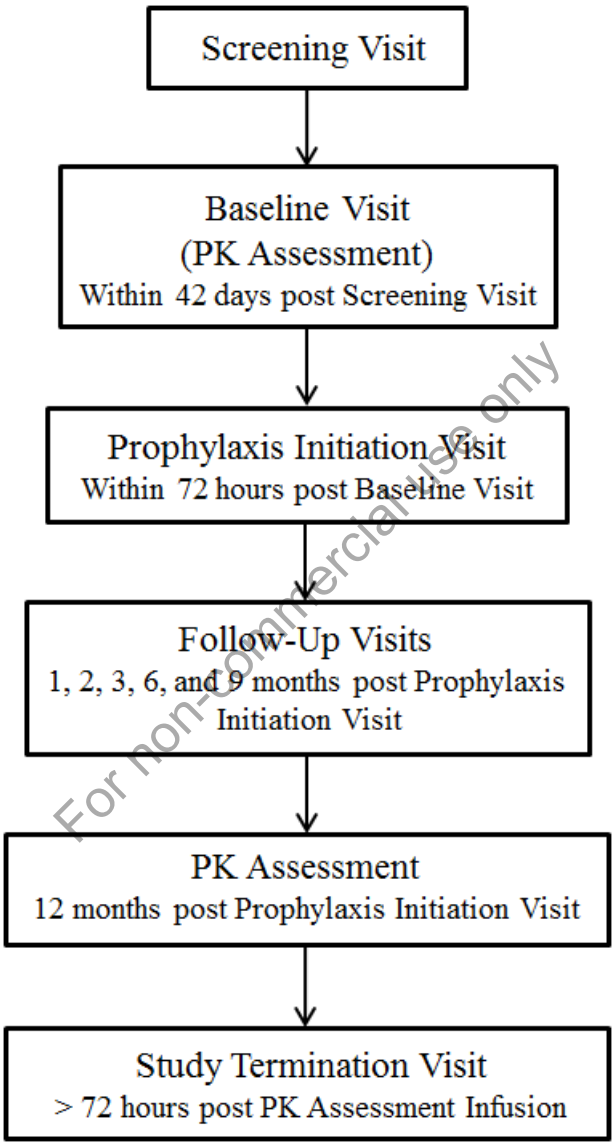
19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the CTA.

20. SUPPLEMENTS

20.1 Study Flow Chart

Figure 1
Study Design for Baxalta Clinical Study 071301



20.2 Schedule of Study Procedures and Assessments

Table 5
Schedule of Study Procedures and Assessments

Procedures/ Assessments	Screening Visit	Baseline Visit (PK-assessment visit)			Prophylaxis Initiation Visit	Interval/Follow-Up Study Visits					PK Assessment and Study Completion			Termination Visit
		Pre-infusion	Infusion	Post-infusion[g]		1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion	Infusion	Post-infusion[g]	Conducted at the 72 hour postinfusion PK Assessment
											12 month± 2 weeks			
Informed Consent [a]	X													
Eligibility Criteria	X													
Medical History[b]	X	X									X			
Medications[c]	X	X			X	X	X	X	X	X	X			X
Non-drug Therapies[c]	X	X			X	X	X	X	X	X	X			X
Physical Exam	X	X			X	X	X	X	X	X	X			X
Adverse Events		X			X	X	X	X	X	X	X			X
Bleeding Episodes	X	X			X	X	X	X	X	X	X			X
Laboratories	X	X		X	X[h]	X	X	X	X	X	X		X	X
Vital Signs[d]	X	X		X	X	X	X	X	X	X	X		X	X
ECG	X								X					X
IP Treatment[e]			X		X	X	X	X	X	X		X		
IP Consumption / Treatment Compliance						X	X	X	X	X				
Subject Diary					X	X	X	X	X	X				
[redacted]	X[f]								X					X

Continued on next page

Continued

[a]) Occurs at enrollment (before screening).
[b]) Including documented history of on-demand treatment for the past 12 months and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 months.
[c]) Including all medications and non- drug therapies taken in the 2 weeks prior to study entry and all the concomitant medications and non-drug therapies during the course of the study.
[d]) Vital signs (pulse rate, respiratory rate, and blood pressure): within 30 minutes before infusion start and 30 ± 15 minutes post-infusion.
[e]) IP treatment after the prophylactic treatment initiation visit at the site will be continued as home-treatment if the subject qualifies; a wash-out period of at least 72 hours is required after the last IP infusion before the follow-up visit. IP infusion will be given at the study site after the blood sample for immunology testing and IR determination is drawn.
[f]) Can be done either at the screening or the baseline visit.
[g]) Time points for blood draws post infusion: 30 ± 5 minutes; 60 ± 5 minutes; 6 ± 1 hours; 12 ± 1 hours; 24 ± 2 hours; 48 ± 2 hours; 72 ± 2 hours.
[h]) If a subject did not undergo PK assessment (for example the subject has participated in the surgery study **071101** and has undergone PK in Study **071101**), laboratory assessments will be performed at this visit.

20.3 Clinical Laboratory Assessments

Table 6
Clinical Laboratory Assessments

Procedures/ Assessments	Screening Visit	Baseline Visit (PK-assessment visit)			Prophylaxis Initiation Visit[k]	Interval/Follow-Up Study Visits					PK Assessment and Study Completion			Termination Visit
		Pre-infusion	Infusion	Post-infusion[g]		1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion	Infusion	Post-infusion[g]	Conducted at the 72 hour postinfusion PK Assessment
											12 month± 2 weeks			
Hematology [a]	X	X		X	X	X	X	X	X	X	X[m]		X	
Clinical Chemistry[b]	X	X		X	X	X	X	X	X	X	X		X	
Coagulation Panel/PK assessment[c]	X	X		X	X	X	X	X	X	X	X		X	
Immunogenicity[d]	X	X		X	X[l]	X	X	X	X	X	X		X	
Viral Serology[e]	X													
Urinalysis[f]	X													
VWD Gene Mutational Analysis / HLA genotype analysis and Analysis of VWF multimers[g]	X													
sP-selectin and D-dimer	X[h]													
Blood Group[i]	X								X					
Pregnancy Test[j]	X													
Exploratory Tests	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Continued on next page

Continued

[a] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. Hematology assessments during PK assessments will be determined prior IP infusion and 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours thereafter.

[b] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin. Clinical chemistry will be determined at baseline, after 24 ± 2 h, 48 ± 2 hours and 72 ± 2 hours during the PK assessments.

[c] Coagulation panel/PK assessment: INR/aPTT, VWF:RCo, VWF:Ag, VWF:CB, FVIII:C, VWF Innovance (exploratory assay); during the PK assessment at the baseline visit blood samples will be drawn 30 min prior PK infusion; once the PK infusion is completed 30 ± 5 minutes; 60 ± 5 minutes; 6 hours ± 1 hour ; 12 ± 0.5 hours; 24 ± 2 hours, 48 ± 2 hours; 72 ± 2 hours and VWF:RCo, VWF:CB, VWF:Ag, VWF Ac, FVIII:C will be determined; in case of thromboembolic event VWF multimers and ADAMTS13 will be analyzed to judge on a possibly relatedness to UHMW fractions of the IP.

[d] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII – Neutralizing and Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG; .CD4* In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined. A washout period of at least 72 hours after the last IP infusion is required before blood samples for immunogenicity assessments can be drawn.

[e] Viral Serology 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; HIV-1/HIV-2 Antibodies

[f] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH

[g] Not required if available in the subject's medical history; VWF multimers: additionally in case of thromboembolic events

[h] At screening and in case of thromboembolic events

[i] Blood group assessment major blood group (local laboratory) only if not available in the subject's medical history

[j] Serum pregnancy test (in females of child-bearing potential if no urine sample is available)

[k] The 72 h post-infusion laboratory assessments coincidence with the initiation visit for prophylactic treatment. After the blood samples are drawn for laboratory assessment for the 72 h post infusion PK assessment, the subject receives the first IP infusion for prophylactic treatment (prophylactic treatment initiation visit).

[l] Only needed for subjects without PK assessment prior to their first IP infusion in this study.

[m] A full PK analysis will be performed. Blood samples will be drawn within 30 minutes pre-infusion, and at 7 time points post-infusion (30 ± 5 minutes, 60 ± 5 minutes, 6 ± 1 hours, 12 ± 1 hours, 24 ± 2 hours, 48 ± 2 hours, 72 ± 2 hours).

20.4 Contraceptive Methods for Female Subjects of Childbearing Potential

In this study, subjects who are women of childbearing potential must agree to utilize a highly effective contraceptive measure throughout the course of the study and for 30 days after the last administration of investigational product. In accordance with the Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials (version 2014-09-15),[ii] birth control methods which may be considered as highly effective include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable[iii]
- Intrauterine device (IUD)[iii]
- Intrauterine hormone-releasing system (IUS) [iii]
- Bilateral tubal occlusion[iii]
- Vasectomised partner(s)[iii]
- Sexual abstinence during the entire study period

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

[ii] Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf.
[iii] Contraception methods that are considered to have low user dependency.

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22. SUMMARY OF CHANGES

Protocol 071301: Amendment 2: 2016 DEC 15

Replaces: Amendment 1: 2016 APR 08

In this section, changes from the previous version of the Protocol, dated 2016 APR 08, are described and their rationale is given.

1. Throughout the document
   Description of Change: Minor grammatical and/or administrative changes have been made.
   Purpose for Change: To improve the readability and/or clarity of the protocol.

2. Title page; Investigator Acknowledgement Page
   Description of Change: NCT number was added.
   Purpose for Change: Administrative.

3. Section 1.1; Investigator Acknowledgement Page
   Description of Change: Changed authorized representative (signatory) / responsible party.
   Purpose for Change: Administrative.

4. Section 2
   Description of Change: Revised reporting method for SAEs to paper SAE form.
   Purpose for Change: Administrative.

5. Section 12.1.1.2
   Description of Change:
   Original text:
   Once determined to meet the criteria for a SUSAR, an SAE should be submitted to regulatory agencies expeditiously.
   New text:
   Once determined to meet the criteria for a SUSAR, ~~an SAE should be submitted to regulatory agencies expeditiously.~~ **the sponsor will ensure expedited SUSAR reporting in line with the regulatory requirements in participating countries as outlined in the Safety Management Plan.**
   Purpose for Change: Administrative.

6. Section 20.4
   Description of Change: New section added: "Contraceptive Methods for Female Subjects of Childbearing Potential"
   Purpose for Change: Section added in order to list what constitutes adequate birth control measures to be used by females of childbearing potential, in line with Clinical Trials Facilitation Group guidance on effective contraception.

INVESTIGATOR ACKNOWLEDGEMENT

RECOMBINANT VON WILLEBRAND FACTOR (rVWF)
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
CLINICAL TRIAL PHASE 3
AMENDMENT 2: 2016 DEC 15
Replaces: AMENDMENT 1: 2016 APR 08

OTHER PROTOCOL ID(s)
NCT Number: NCT02973087
EudraCT Number: 2016-001478-14
IND NUMBER: to be determined

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT

RECOMBINANT VON WILLEBRAND FACTOR (rVWF)

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
CLINICAL TRIAL PHASE 3
AMENDMENT 2: 2016 DEC 15
Replaces: AMENDMENT 1: 2016 APR 08

OTHER PROTOCOL ID(s)
NCT Number: NCT02973087
EudraCT Number: 2016-001478-14
IND NUMBER: to be determined

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date

[redacted], MD
[redacted]
Global Clinical Development Operations
Baxalta US Inc./Baxalta Innovations GmbH

CLINICAL STUDY PROTOCOL

PRODUCT: Recombinant Von Willebrand Factor (rVWF)

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 SHORT TITLE: rVWF IN PROPHYLAXIS

PROTOCOL IDENTIFIER: 071301

CLINICAL TRIAL PHASE 3

GLOBAL AMENDMENT 3: 2017 AUG 03

Replaces: AMENDMENT 2: 2016 DEC 15

ALL VERSIONS:
Amendment 3: 2017 AUG 03
Amendment 2: 2016 DEC 15
Amendment 1: 2016 APR 08
Original: 2014 FEB 09

OTHER ID(s)
NCT Number: NCT02973087
EudraCT Number: 2016-001478-14
IND NUMBER: 013657

Study Sponsor(s):

Baxalta US Inc.
One Baxter Way
Westlake Village, CA 91362
UNITED STATES

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna
AUSTRIA

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted]
Global Clinical Development Operations
Baxalta Innovations GmbH

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (e.g. investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) and suspected unexpected serious adverse events (SUSARs) to the ECs.

ALL SAEs, INCLUDING SUSARs, ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT.

Bleeding events that meet seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) should be reported on the SAE eCRF or SAE Report form as an SAE.

Drug Safety contact information: see SAE Report form
Refer to SAE Protocol Sections and the study team roster for further information.

For definitions and information on the assessment of these events, refer to the following:

- AE, Section 12.1
- SAE, Section 12.1.1.1
- SUSARs, Section 12.1.1.2
- Assessment of AEs, Section 12.1.2

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	Recombinant von Willebrand factor (rVWF)
Name(s) of Active Ingredient(s)	Recombinant von Willebrand factor (rVWF)
CLINICAL CONDITION(S)/INDICATION(S)	
Subjects with severe von Willebrand disease (VWD) requiring prophylactic treatment with coagulation factor replacement	
PROTOCOL ID	071301
PROTOCOL TITLE	A prospective, phase 3, open-label, international multicenter study on efficacy and safety of prophylaxis with rVWF in severe von Willebrand disease
Short Title	rVWF in prophylaxis
STUDY PHASE	Ph3
PLANNED STUDY PERIOD	
Initiation	2016 JUN
Primary Completion	2018 Q1
Study Completion	2018 Q1
Duration	22 months
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
The purpose of this phase 3 study is to investigate the efficacy and safety, including immunogenicity and thrombogenicity, and [redacted] of prophylactic treatment with rVWF in subjects with severe VWD.	
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 and to compare it to the subject's historical ABR for spontaneous bleeding episodes during on-demand treatment.	
Secondary Objectives	
Secondary Objectives are • Additional efficacy assessments of prophylactic treatment • Safety and immunogenicity • Pharmacokinetics (PK) • Efficacy of the treatment of bleeding episodes • Efficacy of the treatment of perioperative bleeding management, if surgery is required	

Exploratory Objectives	
[redacted]	
STUDY DESIGN	
Study Type/ Classification/ Discipline	Efficacy and Safety
Control Type	No control
Study Indication Type	Prophylaxis and treatment of bleeding episodes
Intervention model	Single-group
Blinding/Masking	Open-label
Study Design	This is a phase 3, prospective, open-label, non-randomized, international multicenter study evaluating efficacy, safety, including immunogenicity and thrombogenicity, and [redacted] of prophylactic treatment regimen with rVWF for subjects with severe VWD. Subjects will be offered the option to continue to receive BAX111 in a long-term continuation study.
Planned Duration of Subject Participation	Approximately 15 months
Primary Outcome Measure	
Efficacy • Prospectively recorded ABR for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF and the subjects' historical ABR for spontaneous bleeding episodes during on-demand treatment.	
Secondary Outcome Measure(s)	
Efficacy • Number (proportion) of subjects with reduction of ABR for spontaneous (not related to trauma) bleeding episodes during prophylaxis relative to the subjects' own historical ABR during on-demand treatment. An ABR reduction of >25% is considered relevant. • Number (proportion) of subjects with 0 bleeds during prophylactic treatment with rVWF • Number of infusions and total weight adjusted consumption of rVWF and ADVATE (recombinant factor VIII/rFVIII) per month and per year during prophylactic treatment as well as during on-demand treatment	

Safety

- Adverse events (AEs)
- Incidence of thromboembolic events
- Incidence of severe hypersensitivity reactions
- Development of neutralizing antibodies to VWF and FVIII
- Development of total binding antibodies to VWF and FVIII
- Development of antibodies to Chinese hamster ovary (CHO) proteins, mouse immunoglobulin G (IgG) and rFurin

Pharmacokinetic

- Incremental recovery (IR), terminal half-life ($T_{1/2}$), mean residence time (MRT), area under the curve/dose (AUC/dose), area under moment curve/dose (AUMC/dose), volume of distribution at steady state (Vss) and clearance (CL) based on Von Willebrand factor Ristocetin cofactor activity (VWF:RCo), Von Willebrand factor antigen (VWF:Ag), Von Willebrand collagen binding activity (VWF:CB), and time course (72 hours) of FVIII clotting activity (FVIII:C) levels.

Efficacy of the treatment of bleeding episodes

- Number of infusions of rVWF and ADVATE (rFVIII) per spontaneous bleeding episode
- Number of infusions of rVWF and ADVATE (rFVIII) per traumatic bleeding episode
- Weight-adjusted consumption of rVWF and ADVATE (rFVIII) per spontaneous bleeding episode
- Weight-adjusted consumption of rVWF and ADVATE (rFVIII) per traumatic bleeding episode
- Overall hemostatic efficacy rating at resolution of bleed

Efficacy of treatment of perioperative bleeding management, if surgery is required

- Intraoperative actual versus predicted blood loss (assessed by the operating surgeon) at completion of surgery
- Intraoperative hemostatic efficacy score on a scale of excellent, good, moderate or none (assessed by the operating surgeon) at completion of surgery
- For elective surgery: an overall assessment of hemostatic efficacy 24 hours after the last perioperative infusion of rVWF, assessed by the Investigator
- Daily intra- and postoperative weight-adjusted dose of rVWF with or without ADVATE through postoperative day 14.

Exploratory Outcome Measures

- [redacted]
- [redacted]

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**Dosage form**: lyophilized powder and solvent for solution for injection **Dosage frequency**: Prophylactic Treatment Subjects transitioning from on-demand treatment will be infused twice weekly with BAX 111 (rVWF) at doses of 50 ± 10 IU/kg rVWF:RCo. Dosage may be individualized within this range based on: • the PK data • type and severity of bleeding episodes the subject has experienced in the past • monitoring of appropriate clinical and laboratory measures Any further adjustment will have to be agreed with the sponsor in advance. Treatment of Bleeding Episodes: Dosage must be individualized based on the subject's weight, type and severity of bleeding episode and monitoring of appropriate clinical and laboratory measures. In general, an initial dose of 40-60 IU/kg VWF:RCo with 30-45 IU rFVIII [ADVATE]/kg) is recommended (rVWF:rFVIII ratio of 1.3:1: ± 0.2). In cases of major bleeding episodes, a dose of up to 80 IU/kg VWF:RCo may be infused. Subsequent doses, if necessary, will be administered with or without ADVATE to maintain VWF:RCo and FVIII levels for as long as deemed necessary by the investigator. **Mode of Administration:** intravenous
SUBJECT SELECTION	
Targeted Accrual	Approximately 18 subjects to achieve 15 evaluable subjects with severe VWD
Number of Groups/ Arms/ Cohorts	Single-group

Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding:
   a. Type 1 (VWF:RCo <20 IU/dL) or,
   b. Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2M or,
   c. Type 3 (VWF:Ag ≤3 IU/dL).
2. Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.
3. Subject currently receiving on-demand treatment for whom prophylactic treatment is recommended according to standard of care at the center.
4. Has ≥3 documented spontaneous bleeds requiring VWF treatment during the past 12 months
5. Availability of records to reliably evaluate type, frequency and treatment of bleeding episodes during 12 months of on-demand treatment prior to enrollment.
6. Subject is ≥18 years old at the time of screening and has a body mass index ≥15 but <40 kg/m^2.
7. If female of childbearing potential, subject presents with a negative blood/urine pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.
8. Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

Subjects who meet ANY of the following criteria are not eligible for this study:

1. The subject has been diagnosed with Type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD (e.g., qualitative and quantitative platelet disorders or elevated prothrombin time (PT)/international normalized ratio [INR] >1.4).
2. The subject has received prophylaxis treatment in the 12 months prior to screening (including those who received treatment once a month for menorrhagia but were not treated for any other bleeds).
3. The subject is currently receiving prophylaxis treatment.
4. The subject has a history or presence of a VWF inhibitor at screening.
5. The subject has a history or presence of a FVIII inhibitor with a titer ≥0.4 BU (by Nijmegen modified Bethesda assay) or ≥0.6 BU (by Bethesda assay).
6. The subject has a known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins.
7. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
8. The subject has a medical history of a thromboembolic event.
9. The subject is HIV positive with an absolute Helper T cell (CD4) count <200/mm^3.
10. The subject has been diagnosed with significant liver disease as evidenced by any of the following: serum alanine aminotransferase (ALT) 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).

11. The subject has been diagnosed with renal disease, with a serum creatinine level ≥2.5 mg/dL.
12. The subject has a platelet count <100,000/mL at screening.
13. The subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to signing the informed consent.
14. The subject is pregnant or lactating at the time of enrollment.
15. Patient has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
16. The subject has participated in another clinical study involving another investigational product (IP) or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
17. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
18. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
19. The subject has a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
20. The subject is in prison or compulsory detention by regulatory and/or juridical order
21. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.

Delay criteria

1. If the subject presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) the screening visit will be postponed until the subject has recovered.

STATISTICAL ANALYSIS

Sample Size Calculation

The determination of the sample size for this study is not based on strict statistical considerations. The sample size of a subset of at least 15 subjects with severe VWD, 5 of whom must have Type 3 VWD, is based on the Guideline on the Clinical Investigation of Human Plasma Derived von Willebrand Factor Products (CPMP/BPWG/220/02).[1]

Planned Statistical Analysis

Primary Outcome Measure:

The statistical analysis will provide descriptive summaries.

The prospectively recorded annualized bleeding rate (ABR) of spontaneous (not related to trauma) bleeding episodes during prophylactic treatment will be assessed using negative binomial distribution. Mean ABR of spontaneous bleeding episodes together with the corresponding 95% two-sided confidence intervals (CIs) will be reported for the prospective counts as well as those based on historical data.

Secondary Outcome Measures:

Efficacy:

For the number of infusions and for the total weight adjusted consumption of rVWF and ADVATE per month and per year during prophylactic treatment as well as during on-demand treatment for bleeding episodes, summary statistics will be carried out.

For the number (proportion) of subjects with reduction of ABR relative to historic ABR as well as for the number (proportion) of subjects with 0 bleeds, proportions and corresponding 95% two-sided CIs will be performed. An ABR reduction of >25% is considered relevant.

The cause, type, localization and severity of bleeding episodes will also be recorded and summarized.

Efficacy of the Treatment of Bleeding Episodes:

For the number of infusions of rVWF and ADVATE per bleeding episode, for the weight adjusted consumption of rVWF and ADVATE per bleeding episode as well as for the overall hemostatic efficacy rating at resolution of bleed, summary statistics will be carried out.

The severity and localization of bleeding episodes will also be recorded and summarized. Bleeding episodes should be organized by where they occur in addition to whether they occurred spontaneously or due to a traumatic event.

Efficacy of the Treatment of Perioperative Bleeding Management, if Surgery is Required:

Intraoperative actual versus predicted blood loss and intraoperative hemostatic efficacy score on a scale of excellent, good, moderate or none will be assessed at completion of surgery by the operating surgeon. For elective surgery, an overall assessment of hemostatic efficacy 24 hours after the last perioperative infusion of rVWF will be assessed by the Investigator. Daily intra- and postoperative weight-adjusted dose of rVWF with or without ADVATE will be recorded through postoperative day 14.

Pharmacokinetic:

The PK parameters $AUC_{0\text{-}72h}$/Dose, $AUC_{0\text{-}\infty}$/Dose, $AUMC_{0\text{-}\infty}$/Dose, MRT (mean residence time), CL (clearance), IR (incremental recovery), $T_{1/2}$ (elimination phase half-life), V_{ss} (Volume of distribution at steady state), C_{max} (maximum concentration) and T_{max} (time to reach the maximum concentration) will be summarized by mean, standard deviation and the corresponding 90% CIs, median, Q1, Q3, IQR and range.

Descriptive statistics will be used to summarize VWF:RCo levels for each nominal time point on the PK curve.

For all subjects concentration vs. time curves will be prepared.

Safety:

The number of subjects who experienced SAEs and the number of SAEs will be tabulated. In addition, the number of subjects who experienced AEs assessed as related to IP by the investigator and by the sponsor, and the number of IP-related AEs will be tabulated and subcategorized for thromboembolic events, neutralizing and total binding antibodies to VWF and FVIII, and hypersensitivity reactions by severity, as well as antibodies to Chinese hamster ovary (CHO) proteins, antibodies to mouse immunoglobulin G (IgG) and antibodies to rFurin.

A listing of all AEs will be presented by subject identifier, age, sex, preferred term and 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. An overview table for AEs will be provided, presenting the number of AEs, the number of subjects with AEs and the corresponding percent of subjects in total and by seriousness and relationship to study treatment. An additional summary table will present the total number of (mild, moderate, severe) AEs by system organ class and preferred term with relationship to IP.

Exploratory Outcome Measures:

[redacted]

4. TABLE OF CONTENTS

Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABR	Annualized bleeding rate
ADAMTS13	A Disintegrin And Metalloproteinase with a Thrombospondin type 1 motif, number 13
AE	Adverse event
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC0-∞	Area under the plasma concentration /time curve from time 0 to infinity
$AUC_{0\text{-}72h}$/Dose	Area under the plasma concentration/time curve from time 0 to 72 hours post-infusion/dose
$AUC_{0\text{-}\infty}$/Dose	Area under the plasma concentration/time curve from time 0 to infinity/dose
AUC/Dose	Area under the curve/dose
AUMC	Area under moment curve
$AUMC_{0\text{-}\infty}$/Dose	Area under the first moment curve from time 0 to infinity/dose
aPTT	Activated partial thromboplastin time
B19V	Parvovirus B19
BILI	Bilirubin
BP	Blood pressure
BU	Bethesda Unit
BUN	Blood urea nitrogen
BW	Body weight
CAM	Cell adhesion molecule
CB	Collagen binding activity
CBC	Complete blood count
CD4	Helper T cell
CHO	Chinese hamster ovary
CI	Confidence interval
Cl	Chloride
CL	Clearance
C_{max}	Maximum plasma concentration
CR	Creatinine
CTA	Clinical Trial Agreement
eCRF	Electronic case report form
DMC	Data monitoring committee

Abbreviation	Definition
DIC	Disseminated intravascular coagulation
DVT	Deep vein thrombosis
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
FVIII	Factor VIII
FVIII:C	Factor VIII clotting activity
GCP	Good Clinical Practice
GI	Gastrointestinal
Glu	Glucose
GPIb	Glycoprotein Ib
HAMA	Human anti- mouse antibodies
HAV	Hepatitis A virus
HB	Hepatitis B
HBs	Hepatitis B surface
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
[redacted]	[redacted]
HRP	Horseradish peroxidase
IB	Investigator's brochure
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INR	International normalized ratio
IP	Investigational product
IQR	Interquartil range
IR	Incremental recovery

Abbreviation	Definition
i.v.	Intravenous
K	Potassium
k.o.	Knock out
LDH	Lactate Dehydrogenase
Na	Sodium
NMC	Non-medical complaint
NOAEL	No observed adverse effect level
MRI	Magnetic resonance imaging
MRT	Mean residence time
pdVWF	Plasma derived VWF product
pdVWF/FVIII	Plasma derived VWF product containing fractions of FVIII
PBAC	Pictorial Blood Assessment Chart
PCR	Polymerase Chain Reaction
PEF	Peak expiratory flow
PK	Pharmacokinetic
PKFAS	Pharmacokinetic Full Analysis Set
PKPPAS	Pharmacokinetic Per Protocol Analysis Set
PP	Per protocol
PT	Prothrombin time
Q1, Q3	Quartile
rFVIII	Recombinant factor VIII
rVWF	Recombinant von Willebrand factor
RBC	Red blood cell count
SAE	Serious adverse event
SAER	Serious adverse event report
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
[redacted]	[redacted]
SIC	Subject identification code
sP-selectin	Soluble P-selectin
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Elimination phase half life
TIA	Transient ischemic attack
Tmax	Time to reach the maximum concentration

Abbreviation	Definition
TTP	Thrombotic thrombocytopenic purpura
ULMW	Ultra-large molecular weight
ULN	Upper limit of normal
Vss	Volume of distribution at steady state
[redacted]	[redacted]
VTE	Venous thromboembolism (VTE)
VWD	von Willebrand disease
VWF	Von Willebrand factor
VWF:Ag	Von Willebrand factor antigen
VWF:CB	Von Willebrand Factor collagen binding
VWF:RCo	Von Willebrand factor: Ristocetin cofactor activity
WBC	White blood cell

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

Baxalta US Inc. (hereafter referred to as Baxalta or sponsor) has developed a human recombinant von Willebrand Factor (rVWF), which is co-expressed with recombinant factor VIII (rFVIII) in a Chinese hamster ovary (CHO) cell line and separated during the subsequent downstream process. To address concerns regarding the risk of transmission of blood-borne pathogens that may be introduced by human plasma, no exogenously added raw materials of human or animal origin are employed in the cell culture, purification, or formulation of the final container product. The only proteins present in the final container product other than rVWF are trace quantities of murine immunoglobulin (IgG, from the immunoaffinity purification), host cell (i.e., CHO) protein, rFurin (used to further process rVWF). rVWF is intended for the treatment of von Willebrand disease (VWD).

rVWF has been developed under the Baxalta internal code BAX111 and is used as investigational product (IP) in this study. rVWF may be used with or without ADVATE (rFVIII) for the treatment of bleeding episodes (see Section 8.6.4.4). See Section 8.6 for further information on the IPs and their usage in this study. A detailed description of rVWF is also provided in the Investigator's Brochure (IB).

rVWF was granted licensure in the United States in December 2015 under the brand name VONVENDI for the on-demand treatment and control of bleeding episodes in adults diagnosed with VWD; as of the date of this protocol VONVENDI is not yet available on the market.

6.2 Clinical Condition/Indication

Von Willebrand Factor (VWF) is a large multimeric glycoprotein with a molecular weight that varies from 500 to 20,000 kDa. VWF is normally found in plasma and produced in the alpha-granules of platelets and in endothelial cell organelles known as the Weibel-Palade bodies. VWF mediates platelet adhesion and aggregation at sites of vascular injury, one of the key functions in primary hemostasis. VWF also serves to stabilize coagulation factor VIII (FVIII), where FVIII is an essential cofactor of secondary hemostasis, which leads to fibrin clot formation.[2] Qualitative and/or quantitative deficiencies of VWF lead to a highly variable bleeding diathesis known as VWD, the most common of the hereditary coagulation factor deficiencies. Penetrance of VWD is highly variable, with only a small fraction of mildly affected patients displaying clinical symptoms or a family history of a bleeding diathesis.

The current biochemical-based classification distinguishes disorders arising from partial quantitative (type 1), qualitative (type 2), or virtually complete (type 3) deficiencies of VWF. Up to 70% of VWD patients are diagnosed with type 1 VWD, which may also be associated with minor functional defects in the molecule. In general, patients with type 1 VWD display mild clinical symptoms. Approximately 20 to 30% of VWD patients are diagnosed with type 2 VWD. Type 2 VWD is further divided into 4 subtypes (A, B, N, and M), reflecting distinct classes of functional abnormalities. These defects result in abnormal functional and/or multimeric distribution patterns that facilitate their diagnosis. The bleeding diathesis is usually moderate and primarily affects the mucosal tissues. Type 2N VWD patients are sometimes misdiagnosed as mild hemophilia A. Finally, approximately 1% percent of VWD patients exhibit a total or near total absence of VWF, which is classified as type 3 VWD. The incidence of type 3 VWD is estimated at 0.5-1.0 x 10^6. This type is also associated with a very low FVIII level (typically <5%) because the VWF carrier function for FVIII is lost. Replacement of VWF alone stabilizes endogenous FVIII, resulting in hemostatic levels within several hours post-infusion. Published results from studies of a plasma-derived VWF concentrate demonstrated an increase of FVIII at an approximate rate of 5.8 ± 1 IU dL^{-1} h^{-1}.[3] Type 3 VWD patients display severe hemorrhagic symptoms with bleeding predominantly in mucosal tissues, muscle and joints. All VWD patients, particularly those with type 2 or type 3 VWD, are at an increased risk for life-threatening bleeding episodes.

6.3 The Role of Prophylaxis in the Management of VWD

The goals of long term prophylaxis in VWD are to maintain VWF and FVIII at sufficient levels to reduce the frequency and duration of bleeding episodes, the need for red blood cell transfusions, and the risk of complications, such as arthropathy.[4] In contrast to hemophilia, routine prophylaxis is not as established in VWD, although prophylaxis for patients with severe VWD have already been in use in Sweden during the 1950s.[5] In those early days of VWD treatment plasma FVIII concentrates containing VWF fractions were applied for replacement therapy, which then were followed by plasma derived VWF products containing fractions of FVIII (pdVWF/FVIII).

A Swedish cohort including 37 patients with type 3 VWD under prophylactic median treatment of 11 years (range 2 to 45 years) was retrospectively analyzed.[6,7] The doses used for prophylaxis, given once weekly for at least 45 weeks per year, were calculated based on 12 to 50 IU/kg body weight (BW) of FVIII clotting activity (FVIII:C) which approximately corresponded to 24-100 IU/kg von Willebrand factor: Ristocetin cofactor activity (VWF:RCo) considering that mainly Haemate with a known VWF:RCo/FVIII:C ratio of about 2 was used. An escalation of doses from 1 to 3 dose levels was allowed depending on the frequency and severity of bleeding episodes.

The results demonstrate that under long-term prophylaxis the number of bleeds could be reduced dramatically. Whereas the median value for bleeds per year was about 10 before prophylaxis this value could be reduced to less than 1 bleed per year during prophylaxis.

The benefit of prophylaxis for such indications was retrospectively also demonstrated in a cohort of Italian patients including type 3, 2A, 2M and type 1 patients. Prophylaxis was started after severe gastrointestinal or joint bleeding episodes and completely prevented bleeding episodes in 8 of these 11 patients and largely reduced the need of blood transfusions in the remaining 3. A regimen of 40 IU rVWF:RCo/kg was applied every other day or twice a week. A prospective study on prophylaxis, the PRO.WILL study, has been initiated in Italy.[8]

The results of a prospective study investigating the prophylaxis in children and young adults showed a significantly reduced bleeding frequency and bleeding score (3 vs. 0.07; 3 vs. 0. p<0.001) compared to the pre-prophylaxis values. The median dose was 40 (20-47) IU/kg VWF:RCo administered mainly twice weekly in 23 patients, 3 times a week in 7 patients and 4 times a week in 2 children.[9]

The VWD Prophylaxis Network initiated the VWD International Prophylaxis (VIP) trial to investigate the role of prophylaxis in patients with severe VWD including Type 1, 2, and 3. The dose of the factor replacement product was 50 IU /kgVWF:RCo. The frequency of the dose depended on the type of bleeding and could be increased from once weekly to twice weekly or 3 times per week. For the treatment of menorrhagia the dose of 50 IU/kg VWF:RCo was given on the first day of menses for 2 cycles. The frequency could be increased to Day 1 and 2 for 2 cycles or to Day 1, 2, and 3 of menses.

The study contains both retrospective and prospective study components. Results from the retrospective study component were published, including 61 subjects on prophylactic regimen in the past 6 months prior to enrollment or subjects with a history of prophylaxis over at least 6 month.[10] Differences in annualized bleeding rates (ABR) within individuals (during prophylaxis – before prophylaxis) were significant for those with primary indications of epistaxis (P = 0.0005), joint bleeding (P = 0.002) and gastrointestinal (GI) bleeding (P = 0.001). The difference in the group whose primary indication for treatment was abnormally heavy bleeding at menstruation (n = 4) was not significant (P = 0.25). The reduction of mucosal bleeding likely not only dependents on normal circulating levels of active VWF, but also on the presence of discrete concentrations of normal VWF inside the platelets and within endothelial matrices. The low subject number (n=4) and the treatment scheme for menorrhagia on Days 1, 2, and 3 of menses which might represent rather on-demand than prophylactic treatment may also account for the outcome in this study.

Results from the prospective study component were reported recently.[11] Eleven subjects completed the study. Six subjects had type 2A, and 5 subjects had type 3 VWD. Six subjects presented with epistaxis, 3 with GI bleeding, and 2 with joint bleeding. Seven subjects had dose escalation above the first level. Among the 10 subjects with evaluable bleeding log data, the use of prophylaxis decreased the median ABR from 25 to 6.1 (95% confidence interval [CI] of the rate difference: -51.6 to -1.7), and the median ABR was even lower (4.0; 95% CI: -57.5 to -5.3) when the subjects reached their final dosing level. The authors concluded that this was the first prospective study to demonstrate that prophylaxis with VWF concentrates is highly effective in reducing mucosal and joint bleeding rates in clinically severe VWD.

The results of the VIP study and previous investigations suggest that VWD patients with recurrent bleeding episodes and severe menorrhagia will benefit from a prophylactic VWF replacement therapy. There is evidence that up to 40% of patients with type 3 VWD experience joint bleeding which can lead to hemophilic arthropathy. Other potential indications for prophylaxis include patients with type 2A or 2B VWD with recurrent gastrointestinal bleeding, menorrhagia or frequent epistaxis.[4] Long-term prophylaxis for most patients with type 3 VWD and in some patients with type 1 or 2 VWD, depending on the pattern of bleeding, may be the treatment option of choice. Although the main experience with long-term prophylaxis is with secondary prophylaxis, primary prophylaxis starting at young age is recommended to prevent arthropathy in patients with severe VWD.[12]

However, further studies are needed to develop evidence-based guidelines for prophylactic treatment in VWD.

6.4 Population to be Studied

A total of approximately 18 eligible, adult subjects to achieve approximately 15 evaluable subjects with severe VWD are planned to be enrolled, of which a subset of at least 5 subjects will have type 3 VWD. Enrolled subjects (i.e., subjects who have signed the informed consent form) will be eligible to participate in the study if they meet all of the inclusion criteria (see Section 9.1) and none of the exclusion criteria (see Section 9.2).

6.5 Findings from Nonclinical and Clinical Studies

The following summarizes the key findings from relevant nonclinical studies as well as from the completed clinical studies **070701** (Phase 1 PK and safety in VWD), **071001** (Phase 3 safety and efficacy in the treatment of bleeding episodes in VWD), **071104** (Phase 1 safety and PK in hemophilia A), and **071401** (Phase 3, expanded access in a single subject with VWD). Potential risks and efficacy of rVWF:ADVATE are summarized in the following sections. For additional information on nonclinical and clinical Phase 1 results refer to the rVWF IB.

6.5.1 Findings from Nonclinical Studies

6.5.1.1 Primary Pharmacodynamics

Efficacy of rVWF combined with ADVATE was shown in VWD animal models, which have also low endogenous FVIII levels. Time to occlusion and stable thrombus formation was assessed in the carotid occlusion model in VWD mice. The results demonstrated that rVWF in combination with ADVATE acted efficiently in a dose-dependent manner and had higher efficacy than rVWF alone or plasma derived (pd)VWF. These results were confirmed in an additional study assessing blood loss and survival in a tail tip bleeding model in VWD mice. In a VWD dog rVWF stabilized canine FVIII in the circulation and significantly reduced the bleeding time.

6.5.1.2 Safety Pharmacology

The anaphylactoid and thrombogenic potential of the co-infusion of ADVATE and rVWF and the co-infused product's effects on blood pressure, cardiac and respiratory function and parameters of coagulation activation were investigated in 4 in vivo studies in different animal models. Safety pharmacology studies in rats, guinea pigs, rabbits, and dogs revealed no risks for anaphylactoid and thrombogenic potential of ADVATE in combination with rVWF. All observations in safety pharmacology studies are considered to lie within the biological variability of animal models or occurred due to known species-specific anaphylactoid effects of excipients.

6.5.1.3 Pharmacokinetics

Pharmacokinetic studies of both rVWF alone and combined with human rFVIII (rVWF+ADVATE) were conducted in VWD mice, VWD dogs, VWD pigs, rats, and cynomolgus monkeys. Human rVWF stabilized the endogenous FVIII in VWD mice, VWD pigs, and VWD dogs. Furthermore, the hypotheses that the area under the curve (AUC) with rVWF alone and rVWF+ADVATE is not inferior to the AUC with pdVWF (Haemate P) was tested and confirmed statistically in normal rats.

The pharmacokinetic (PK) characteristics of ADVATE were not affected by co-administration of rVWF in cynomolgus monkeys. The PK data in the FVIII knock out (k.o.) mice model are inconclusive and might not be relevant for the clinical situation. However, a stabilizing effect of VWF on FVIII could be shown in a double knock out model in a dose dependent manner.

6.5.1.4 Toxicology

Single dose toxicity studies were conducted in C57BL/6J-mice, VWD mice, rats, rabbits, and cynomolgus monkeys. Rats, rabbits, and cynomolgus monkeys showed no signs of toxicity. Signs of microthrombosis, an exaggerated pharmacological effect, were observed in mice. Mice are not capable of sufficiently cleaving the rVWF subunit as murine disintegrin and metalloproteinase with a thrombospondin type 1 motif, number 13 (ADAMTS13) does not decrease the ultra-large molecular weight multimers of rVWF.[13] The observed symptoms of microthrombosis are interpreted as a species-specific exaggerated pharmacological effect. Studies evaluating the safety of repeated administration of rVWF with or without ADVATE (daily over 14 days) were performed in a rodent (rat) and non-rodent (cynomolgus monkey) species. Reversible signs of exaggerated pharmacological effects (regenerative anemia, thrombocytopenia, and treatment-related histopathologic changes in the heart, liver, and spleen) were observed in rats that were administered 1400 U VWF:RCo/kg /day + 1080 IU ADVATE/kg/day intravenously once daily for 14 days. Also, these findings are interpreted as a species-specific exaggerated pharmacological effect due to the low susceptibility of human rVWF to cleavage by rodent ADAMTS13.[13] No toxicologically relevant changes were evident for clinical observations, body weight, feed consumption, ophthalmology, urinalysis, coagulation, and serum chemistry parameters, platelet aggregation, and gross pathology. rVWF combined with ADVATE was well tolerated in cynomolgus monkeys after daily intravenous (i.v.) (bolus) administration of 100 U VWF:RCo/kg rVWF combined with 77 IU/kg ADVATE over a period of 14 days. No adverse effects could be detected in this species. There were no signs of hemolysis, thrombosis, or thrombocytopenia after repeated intravenous application of rVWF with or without ADVATE. Therefore, 100 U VWF:RCo/kg/day rVWF with or without 77 IU/kg ADVATE was considered the no observed adverse effect level (NOAEL) in this study, which was the highest dose tested. Anti-drug antibodies, however, were formed in both species and resulted in a significant reduction in drug exposure after 14 applications as compared to a single application. These antibodies substantially reduced the systemic exposure to the test substance as compared to a single dose administration. No adverse effects due to antibody formation were observed in both species.

rVWF combined with ADVATE was well tolerated locally and no genotoxic potential was evident after 2 in vitro and 1 in vivo genotoxicity study. A study on the influence of co-administration of VWF and ADVATE on the immunogenicity of ADVATE in 3 different hemophilic mouse models (E17 hemophilic Balb/c mice, E17 hemophilic C57BL/6J mice, and E17 hemophilic human F8 transgenic mice) showed that rVWF does not negatively impact the immunogenicity of ADVATE in any of the three different hemophilic mouse models.

6.5.2 Findings from Clinical Studies

Two phase 1 studies with rVWF either alone or co-administrated with ADVATE in patients with VWD **070701** and Hemophilia A **071104** and 1 phase 3 study with rVWF in patients with VWD **071001** have been conducted and the results were analyzed and evaluated. Details on study design, populations enrolled, and safety and efficacy outcomes of these 2 phase 1 studies are presented in Section 6.5.2.1 and Section 6.5.2.2, and the phase 3 study in Section 6.5.2.3. Information on a single subject with VWD in Study **071401** is presented in Section 6.5.2.4.

Refer to rVWF IB for periodic updates from other rVWF studies.

6.5.2.1 Study 070701

Phase 1 clinical study **070701** was a multicenter, controlled, randomized, single-blind, prospective 3-step, dose escalation study to investigate safety, tolerability, and PK of rVWF combined at a fixed ratio with ADVATE (VWF:RCo/FVIII:C of 1.3 ± 0.2:1) in adults with severe VWD.[14] Subjects were enrolled in sequential cohorts in a dose escalating manner: Cohort 1, 2, and 3 received a single intravenous infusion of rVWF:ADVATE at the following doses: 2 IU/kg VWF:RCo (Cohort 1), 7.5 IU/kg VWF:RCo (Cohort 2), and 20 IU/kg VWF:RCo (Cohort 3). Subjects in Cohort 4 received a single intravenous infusion of rVWF:ADVATE and pdVWF/ADVATE at 50 IU/kg VWF:RCo in random order.

The primary endpoint was the tolerability and safety after single dose injections of rVWF:ADVATE at 2, 7.5, 20, and 50 IU/kg VWF:RCo for up to 30 days after the last IP infusion. The data generated in this phase 1 study suggest that rVWF:ADVATE up to the highest investigated dose of 50 IU/kg VWF:RCo is well tolerated and safe in adults with severe VWD. No thrombogenic risk or TTP-like syndrome was observed, and no neutralizing antibodies to VWF or FVIII were identified. There were no deaths or other serious adverse reactions, and no infusions were interrupted or stopped due to an AE.

Overall, the reported AE profile was similar between the recombinant and plasma-derived concentrates.

Secondary endpoints were the PK assessment of VWF:RCo, von Willebrand factor antigen (VWF:Ag) and multimeric composition of rVWF as well as FVIII:C at standardized time points after single injections of rVWF:ADVATE and pdVWF:FVIII.

The median VWF:RCo half-life ($T_{1/2}$) of rVWF at the 50 IU/kg dose was 16 hours. $T_{1/2}$ with pdVWF:FVIII at the same dose level appeared shorter at 12.58 hours, however, the limits of the 90% CI were similar (11.73 to 17.7 hours vs. 11.87 to 18.03 hours). The median half-lives of VWF:RCo were shorter with the lower investigated doses: 7.13 hours and 13.23 hours with the 7.5 IU/kg and 20 IU/kg doses, although these data were derived from a much smaller number of subjects.

In consequence of the missing ADAMTS13 cleavage, ultra-large molecular weight (ULMW) multimers are contained in the rVWF final product. The immediate cleavage of these ultra-large multimers by ADAMTS13 upon release into the circulation could be demonstrated applying sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE)/Immunoblot with polyclonal anti-VWF antibodies to detect the resulting rVWF subunit cleavage fragments.

Overall the data generated in this phase 1 study suggest that rVWF:ADVATE is well tolerated and safe in adults with severe VWD.

6.5.2.2 Study 071104

This study was a prospective, uncontrolled, non-randomized, multicenter proof of concept study to assess safety and PK of the addition of rVWF to ADVATE treatment in 12 evaluable subjects with severe hemophilia A. All subjects underwent 3 PK analyses: the first after infusion with ADVATE alone, the second after infusion with ADVATE plus 10 IU/kg rVWF and the third after infusion with ADVATE plus 50 IU/kg rVWF.

The PK analysis was performed at intervals of approximately 8 to 14 days. Before each infusion for PK assessment, there was a wash-out period of at least 5 days and the subjects were not actively bleeding.

Primary outcome measures indicate that co-administration of rVWF slightly sustain ADVATE activity with the highest observed ADVATE half-life of 13.74 h (CI 11.44 to 16.52) after co-infusion of 50 IU/kg ADVATE plus 50 IU/kg rVWF:RCo.

The highest improvement in ADVATE circulating half-life was observed in subjects with VWF:Ag levels below 100% which indicates an association between baseline VWF:Ag levels and ADVATE half-life increase.

No treatment related adverse events (AEs) or serious adverse events (SAEs) were reported. No subject withdrew due to an AE and there were no deaths. No binding antibodies to VWF, CHO, and rFurin were detectable in the confirmatory assay and no signs of a hypersensitivity to rVWF or ADVATE antigen were observed. Laboratory values over time did not indicate any potential safety risk for hemophilia A patients treated with rVWF and ADVATE in combination.

In summary, the data indicate that rVWF co-administered with ADVATE up to the highest dose of 50 IU/kg VWF:RCo is well tolerated and safe in hemophilia A patients.

6.5.2.3 Study 071001

This was a phase 3, multicenter, open-label, part-randomized clinical study to assess the PK, safety, and efficacy of rVWF:rFVIII and rVWF in the treatment of bleeding episodes in adult subjects with severe type 3 and severe non-type 3 VWD.[15] A total of 49 subjects were enrolled (signed informed consent) and screened, 18 subjects were randomized (Arm 1 and Arm 2 [PK 50] only), 37 subjects were treated with IP (all study arms), and 30 subjects completed the study.

The study consisted of 2 parts (Part A and Part B). Part A consisted of PK assessments alone (Arm 2: PK50 only [without treatment of bleeding episodes]), or PK assessments (Arm 1: PK50 and Arm 3: PK80) plus on-demand treatment period(s) of 6 months for bleeding episodes, or on-demand treatment for bleeding episodes only (Arm 4). Subjects receiving treatment for PK assessments and/or bleeding episodes in Part A were to be entered into Part B to continue on-demand treatment for bleeding episodes for 6 additional months for a total of 12 months in the study.

The primary outcome measure was the number of subjects with “treatment success” (extent of control of bleeding episodes), which was defined as a mean efficacy rating score of <2.5 for a subject’s IP-treated bleeding episodes during the study. The rate of subjects with treatment success was 100% (Clopper-Pearson exact 90% CI: 84.7 to 100.0) for bleeds where the assessments were made prospectively and excluding GI bleeds. Sensitivity analyses confirmed the results of the primary analysis.

Crossover results at 50 IU/kg VWF:RCo showed that the PK profile for rVWF VWF:RCo was independent of administration alone or with rFVIII (ADVATE) ($T_{1/2}$: 19.4 hours for rVWF and 16.6 hours for rVWF:rFVIII; IR: 1.8 U/dL per IU/kg infused for both rVWF and rVWF:rFVIII; MRT: 26.7 hours for rVWF and 25.2 hours for rVWF:rFVIII). FVIII levels increased substantially with a median peak at 24 hours of 111.0 U/dL for rVWF:rFVIII and 86.0 U/dL after rVWF alone, indicating that rVWF induces a sustained increase in endogenous FVIII activity. The rVWF PK profile was comparable at 50 IU/kg and 80 IU/kg VWF:RCo, and repeated PK at 80 IU/kg VWF:RCo showed close agreement between pretreatment and end-of-study results.

Further analysis of the PK data from the **071001** study supports the initial use of 50 IU/kg twice weekly for prophylaxis dosing in the present study for those subjects who are moving from on-demand to prophylaxis. Using 50 IU/kg for PK measurements, subjects in the **071001** study exhibiting a $T_{1/2}$ for rVWF of 14, 16, or 19 hours had BAX111 plasma concentrations at 72 hours after administration of 2.55, 4.01, and 6.49% above baseline, respectively, and plasma concentrations at 96 hours after administration of 0.78, 1.40, and 2.71% above baseline, respectively. Subjects who have significant spontaneous bleeding while on twice weekly prophylaxis will have their regimen increased to 50 IU/kg 3 times per week (see Section 8.6.4.2).

A total of 125 AEs occurred in 25/37 (67.7%) subjects (62/318 infusions [19.5%]) during or after infusion with IP. Of these, 116/125 were non-serious (all mild or moderate; none were severe), and 9 SAEs were reported in 7 subjects. Of 125 total AEs, 38 were temporally associated with IP; 8 AEs were considered causally related to IP: 6 non-serious related AEs (tachycardia, infusion site paraesthesia, electrocardiogram [ECG] t-wave inversion, dysgeusia, generalized pruritis, and hot flush) occurred in 4 subjects, and 2 related SAEs (chest discomfort and increased heart rate) occurred in 1 subject. No deaths occurred during this study.

None of the subjects developed anti-VWF or anti-FVIII neutralizing antibodies and no binding antibodies to VWF or rFurin, or antibodies against CHO protein or anti-Murine IgG were observed. No clinical or subclinical signs or symptoms of a thrombogenic event were observed in this study. Following an initial increase in ultralarge VWF multimers after administration of rVWF, a notable decrease in the proportion of large VWF multimers occurred between 12 and 24 hours post infusion, due to degradation by the endogenous ADAMTS13 followed by a continued decline until the end of the 96-hour follow-up period.

Overall, the data support the safe and effective use of rVWF with or without FVIII (ADVATE) in the treatment of bleeds in patients with VWD.

6.5.2.4 Study 071401: Single Subject with von Willebrand Disease

One subject who exhibited allergic reactions to currently marketed pdVWF products was treated in the single-subject study **071401** with rVWF only for the bleed treatment of continued hematuria, and for biopsy and surgical resection of a left-kidney mass.

For the initial rVWF infusion, the subject received a test dose of 5% of the total dose of 60 IU/kg rVWF:RCo at an infusion rate of 1 mL/min. After a 10 to 15-minute observation period, no adverse symptoms or signs were noted and the subject received the remaining 95% of the total dose. The subject was monitored for any signs of an allergic reaction, and none were noted. Treatment with rVWF every 12 to 24 hours was to continue at the discretion of the investigator based on VWF levels and clinical symptomatology. The subject had an excellent response and recovery, which allowed for daily dosing of rVWF and, within 24 hours, the subject's bleeding had stopped. Daily dosing of rVWF was maintained and the subject received his last dose on [redacted].

The subject also received rVWF for 7 days for prophylaxis for surgery (surgical resection of a left-kidney mass). The subject experienced no hemorrhagic complications and no AEs that were considered related to the use of rVWF.

6.6 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

Current treatment of VWD patients relies on desmopressin and VWF products manufactured from pooled human plasma. Human VWF produced by recombinant technology could offer a new perspective in treatment of VWD. The benefit for the individual subject is anticipated to be significant during this clinical study. He/she may benefit from a product that minimizes excessive FVIII administration. Variations in VWF multimeric composition may lead to variability with respect to treating or preventing bleeds in VWD subjects, especially mucosal bleeds which are especially problematic. rVWF product manufactured by Baxalta consistently contains ultra-large molecular weight (ULMW) VWF multimers due to the fact that the product has not been exposed to ADAMTS13. The initial presence of these ULMW VWF multimers, which are subsequently cleaved by the subject's endogenous ADAMTS13, may result in improved platelet and collagen binding and therefore provide more predictable treatment outcomes.

By using a recombinant product, the risk of contamination with blood derived viruses or variant Creutzfeldt-Jakob Disease associated with the use of products of human or animal origin has been virtually eliminated. At this stage of product development, the key societal benefit is a better understanding of advanced treatment options for VWD and enhanced product availability.

These benefits outweigh the following potential risks of rVWF:

- allergic-type hypersensitivity reactions as with any intravenous protein product
- the occurrence of thromboembolic events
- the development of neutralizing antibodies to VWF

Refer to the IB for further details on benefits and risks of the IP.

6.7 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives 2001/20/EC and 2005/28/EC, and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of this phase 3 study is to investigate the efficacy and safety, including immunogenicity and thrombogenicity, and [redacted] of prophylactic treatment with rVWF in subjects with severe VWD.

7.2 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 and to compare it to the subject's historical ABR for spontaneous bleeding episodes during on-demand treatment.

7.3 Secondary Objectives

Secondary Objectives are:

- Additional efficacy assessments of prophylactic treatment
- Safety and immunogenicity
- Pharmacokinetics
- Efficacy of the treatment of bleeding episodes
- Efficacy of the treatment of perioperative bleeding management, if surgery is required

7.4 Exploratory Objectives

7.4.1 [redacted]

8. STUDY DESIGN

8.1 Overall Study Design

This is a prospective, open label, uncontrolled, non-randomized, international, multicenter phase 3 study to evaluate efficacy, safety, including immunogenicity and thrombogenicity, and [redacted] of a prophylactic treatment regimen with rVWF in patients with severe VWD.

Subjects transitioning from on-demand treatment will be infused twice weekly with BAX 111 (rVWF) at doses of 50 ± 10 IU/kg rVWF:RCo. The dose may be adjusted within this range based on the PK data, subject's history of bleeding episodes, and the results from clinical and laboratory assessments (see Section 8.6.4.2).

The overall duration of prophylactic treatment per subject will be 12 months.

During this period any bleeding episodes requiring substitution therapy with VWF concentrate to control bleeding will be treated with rVWF with or without ADVATE. The dose will be according to the bleeding severity and it will be adjusted to the clinical response (see Section 8.6.4.4.2).

The overall study design is illustrated in Figure 1.

8.2 Duration of Study Period(s) and Subject Participation

The overall duration of the study is approximately 22 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The subject participation period is approximately 15 months from enrollment to completion (i.e, last study visit), unless the subject is prematurely discontinued.

Subjects will be offered the option to continue to receive BAX111 in a long-term continuation study.

8.3 Outcome Measures

8.3.1 Primary Outcome Measure

The primary outcome measure is

- Efficacy:
  - Prospectively recorded ABR for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF and the subjects' historical ABR for spontaneous bleeding episodes during on-demand treatment.

8.3.2 Secondary Outcome Measures

8.3.2.1 Efficacy

- Number (proportion) of subjects with reduction of ABR for spontaneous (not related to trauma) bleeding episodes during prophylaxis relative to the subjects' own historical ABR during on-demand treatment. An ABR reduction of >25% is considered relevant.
- Number (proportion) of subjects with 0 bleeds during prophylactic treatment with rVWF
- Number of infusions and total weight adjusted consumption of rVWF and ADVATE per month and per year during prophylactic treatment as well as during on-demand treatment.

8.3.2.2 Safety

- AEs
- Incidence of thromboembolic events
- Incidence of severe hypersensitivity reactions
- Development of neutralizing antibodies to VWF and FVIII
- Development of total binding antibodies to VWF and FVIII
- Development of antibodies to Chinese hamster ovary (CHO) proteins, mouse immunoglobulin G (IgG) and rFurin

8.3.2.3 Pharmacokinetics

- Incremental recovery (IR), terminal half-life ($T_{1/2}$), mean residence time (MRT), area under the curve/dose (AUC/dose), area under moment curve/dose (AUMC/dose), volume of distribution at steady state (Vss) and clearance (CL) based on Von Willebrand factor Ristocetin cofactor activity (VWF:RCo), Von Willebrand factor antigen (VWF:Ag), Von Willebrand collagen binding activity (VWF:CB), and time course (72 hours) of FVIII clotting activity (FVIII:C) levels.

8.3.2.4 Efficacy of the Treatment of Bleeding Episodes

- Number of infusions of rVWF and ADVATE (rFVIII) per spontaneous bleeding episode
- Number of infusions of rVWF and ADVATE (rFVIII) per traumatic bleeding episode

- Weight-adjusted consumption of rVWF and ADVATE (rFVIII) per spontaneous bleeding episode
- Weight-adjusted consumption of rVWF and ADVATE (rFVIII) per traumatic bleeding episode
- Overall hemostatic efficacy rating at resolution of bleed

8.3.2.5 Efficacy of treatment of perioperative bleeding management, if surgery is required

- Intraoperative actual versus predicted blood loss (assessed by the operating surgeon) at completion of surgery
- Intraoperative hemostatic efficacy score on a scale of excellent, good, moderate or none (assessed by the operating surgeon) at completion of surgery
- For elective surgery: an overall assessment of hemostatic efficacy 24 hours after the last perioperative infusion of rVWF, assessed by the Investigator
- Daily intra- and postoperative weight-adjusted dose of rVWF with or without ADVATE through postoperative day 14

8.3.3 Exploratory Outcomes Measure

[redacted]

8.4 Randomization and Blinding

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

8.5 Study Stopping Rules

This study will be stopped if 1 or more of the following criteria are met:

1. Two subjects develop a thromboembolic event
2. Two subjects develop severe hypersensitivity reactions (e.g., clinically significant localized urticaria, generalized urticaria, wheezing, or anaphylaxis); or infusion related tightness of the chest or hypotension
3. Two subjects develop signs and symptoms, suggestive of a thrombotic thrombocytopenic purpura-like syndrome (subjects with type 2B VWD developing thrombocytopenia or changes of the platelet count as described below, will be evaluated on case by case, whether they need to be accounted for), such as
    - A drop in platelet count of 50% of subject's baseline or less than 100.000 per microliter
    - 3-fold increase in lactate dehydrogenase (LDH)
    - Impaired renal function as determined by:
        - Creatinine increase of 1.5-fold from baseline levels
        - Blood urea nitrogen (BUN) increase from normal levels to a level > 60 mg/dL
4. Any subject has abnormal liver function:
    - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations >5 times upper limit of normal (ULN) in the absence of a concomitant bilirubin increase
    - ALT and/or AST elevations >3 times ULN in the presence of a total bilirubin increase >2 times ULN or an international normalized ratio (INR) >1.5 without findings of cholestasis or other alternate etiology to explain the elevations (i.e., "Hy's Law cases")
    - ALT and/or AST elevations >3 times ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
5. Two subjects develop rVWF neutralizing antibodies

The study may be stopped at any time by the sponsor.

The sponsor ultimately will decide whether to terminate, temporarily halt or modify the study based on the data monitoring committee (DMC) recommendation.

8.6 Investigational Product(s)

8.6.1 Packaging, Labeling, and Storage

8.6.1.1 rVWF (Recombinant von Willebrand Factor)

rVWF will be packaged in boxes with 2 glass vials, one containing the lyophilized rVWF, and the second vial containing the diluent. Further details are provided in the IB and Pharmacy Manual. The rVWF label will include, at a minimum, the actual VWF:RCo potency and the date of expiration.

rVWF should be refrigerated (2-8°C [36-46°F]) in lyophilized form. Deviations from the storage condition have to be communicated and followed up with the sponsor. Inadequately stored product will have to be placed in quarantine and may only be used after written investigational product administration authorization by the sponsor. After removal of the product from the refrigerator the product must not be returned to the refrigerator and has to be used immediately. rVWF must not be used beyond the expiration date printed on the vial. Avoid freezing at all times.

8.6.1.2 rFVIII (Recombinant Factor VIII /ADVATE)

ADVATE will be packaged in boxes with 2 glass vials, one containing the lyophilized rFVIII, and the second vial containing the diluent. Further details are provided in the IB and Pharmacy Manual. The ADVATE label will include, at a minimum, the actual FVIII:C potency and the date of expiration.

ADVATE should be refrigerated (2-8°C [36-46°F]) in powder form and should not be used beyond the expiration date printed on the vial. Deviations from the storage condition have to be communicated and followed up with the sponsor. Inadequately stored product will have to be placed in quarantine and may only be used after written investigational product administration authorization by the sponsor. After removal of the product from the refrigerator the product must not be returned to the refrigerator and has to be used immediately. Avoid freezing at all times.

8.6.2 Reconstitution

The reconstitution procedures for both rVWF and ADVATE products are detailed in the Pharmacy Manual.

8.6.3 Administration

Following reconstitution, rVWF and ADVATE (in case of bleeding episode treatment) should be administered to study subjects at room temperature and within 3 hours of reconstitution. The reconstituted rVWF and ADVATE, should be inspected for particulate matter and discoloration prior to administration, whenever the solution and container permit. The solution should be clear and colorless in appearance. If not, do not administer the product. Plastic syringes provided by the sponsor must be used since coagulation factors tend to stick to the surface of glass syringes.

Investigational product infusions should be given at a rate which should not exceed 4 mL/minute. The investigator/ subject shall ensure that no visible residual volume remains in the syringe(s) and that the complete content is administered. Upon completion of the infusion, the butterfly catheter should be flushed with at least 2 mL of saline solution. In case of a (central) venous access device, the flush should be with at least 10 mL of saline solution. The IP infusions should be administered over a duration of 2 to 15 minutes, depending on the volume.

Only the actual potencies of rVWF and ADVATE as stated on the vial labels and described in the Pharmacy Manual should be used. A variation of up to 10% of the intended dose for prophylactic infusions and of the intended dose for treatment of bleeding episodes is permissible and the exact dose should be recorded on the Case Report Form (CRF).

At study visits where recovery analysis is being done, vials with the same lot numbers should be used throughout the PK IP infusion per subject.

For treatment of bleeding episodes there are 2 options for the preparation of rVWF and ADVATE for infusion if needed.

Preferably sequential administration will be done: separate syringes of the appropriate dose of rVWF and ADVATE will be prepared for sequential infusion. rVWF should be infused first sequentially followed preferably within 10 minutes by infusion of ADVATE. Only the actual potencies of rVWF and ADVATE as stated on the vial labels and described in the Pharmacy Manual should be used.

Alternatively, premixed solutions can be administered: rVWF and ADVATE will be an i.v. admixture in a single syringe to achieve the appropriate dose. The contents of each vial of rVWF or ADVATE can be drawn into 1 syringe by using a separate unused reconstitution device as described in the Pharmacy Manual.

The final dose of rVWF:ADVATE should be at a ratio of 1.3:1 ± 0.2.

8.6.4 Description of Treatment

8.6.4.1 Baseline Visit (PK-Assessment Treatment)

The first IP infusion for PK assessment should be within 42 days after the completion of screening procedures and confirmation of eligibility.

At the baseline visit the subjects will receive a dose of 50 ± 5 IU/kg rVWF:RCo for PK assessment. 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).

Subjects previously enrolled in rVWF studies **070701**, **071001** or **071101** and having previously undergone PK assessments in these studies are required to repeat the PK assessment due to different dose and time points used in these former studies (see Section 12.9.1 and Section 20.3). A washout period of at least 5 days is required prior to infusion of rVWF for PK assessment for subjects previously treated with rVWF.

8.6.4.2 Prophylaxis Initiation Treatment

The prophylaxis initiation treatment visit will coincide with the 96 ± 2 h PK assessment. At this visit subjects will receive their prophylaxis initiation dose of 50 ± 10 IU/kg rVWF:RCo after the blood draw for the 96 ± 2 hours post-infusion PK assessment. If subjects do not need an additional PK assessment, subjects must receive the IP for prophylaxis initiation treatment within 42 days after screening and confirmation of eligibility. The exact standard prophylaxis dose may range between 40 and 60 IU/kg based on:

- available historical PK data
- type and severity of bleeding episodes the subject has experienced in the past and
- monitoring of appropriate clinical and laboratory measures

Dose adjustments during the continued prophylactic treatment are described in Section 8.6.4.3.

The subject will be trained on IP reconstitution and administration and may then qualify for home treatment (see Section 8.6.4.3.2). Refer to Table 6 for study procedures and Table 8 for clinical laboratory assessments.

8.6.4.3 Prophylaxis Treatment

The standard prophylactic dose is 50 ± 10 IU/kg rVWF:RCo. All subjects will initially receive BAX111 (rVWF) twice per week (Table 1, Schedule A). Examples of all dosing schedules are provided in Table 1.

Table 1
rVWF Dosing Schedule Examples: Schedules A and B

Example	M	T	W	Th	F	Sat	Sun	M	T	W	Th	F	Sat	Sun
Schedule A	X			X				X			X			
Schedule B	X		X			X		X		X			X	

Dose and frequency adjustments will be agreed with the sponsor in advance unless it constitutes an urgent safety measure. Dose adjustments to higher doses (not exceeding the upper dose limit of 80 IU/kg rVWF:RCo) and adjustments to frequency will only be allowed in cases of persisting high bleeding rates due to insufficient therapeutic response.

8.6.4.3.1 Treatment Escalation

Criteria for dose and frequency escalation are specific to each bleeding indication (Table 2) but, overall, involve 1 significant breakthrough bleeding episode despite compliant prophylaxis. Subjects entering the study will begin prophylaxis treatment according to Schedule A (Table 1) and will remain at this dose and frequency until meeting the criteria for escalation to the next higher schedule: for example, from 2 infusions of 50 ± 10 IU VWF:RCo/kg/week to 3 infusions of 50 ± 10 IU VWF:RCo/kg/week (Schedule B) to achieve adequate prophylaxis.

Table 2
Criteria for Escalation Specific to Each Bleeding Indication

	Schedule A	Schedule B
Joint bleeding	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a spontaneous joint bleeding episode occurs while on this regimen, the subject will escalate to Schedule B following its resolution	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
GI bleeding	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a severe GI bleeding episode occurs while on this regimen, the subject will escalate to Schedule B following its resolution	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Menorrhagia	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) on days 1 and 2 of menses for 2 cycles. Menstrual flow will be monitored by the PBAC score. If the average pictorial chart score is > 185, then the subject will escalate to Schedule B	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) on days 1, 2, and 3 of menses. Menstrual flow will be monitored by the PBAC score.
Epistaxis	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. The subject will escalate to Schedule B in the event of 1 occurrence of breakthrough bleeding requiring intervention such as iron replacement therapy, transfusion, packing, hospitalization; or 2 bleeding events that require treatment with factor replacement	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Oral and Other Mucosa	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. The subject will escalate to Schedule B in the event of 1 occurrence of breakthrough bleeding requiring intervention such as iron replacement therapy, transfusion, packing, hospitalization; or 2 bleeding events that require treatment with factor replacement.	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Muscle and Soft Tissue	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a spontaneous bleeding episode occurs while on this schedule, the subject will escalate to Schedule B following its resolution.	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.

Abbreviations: GI: gastrointestinal; PBAC: Pictorial Blood Assessment Chart.

Dose and frequency reduction will only be allowed in case plasma VWF or FVIII levels are exceeding the recommended ranges.

If a subject does not adequately respond to rVWF therapy, he/she will be evaluated for the presence of neutralizing and total binding anti-VWF antibodies (see Section 12.9.3.2).

If a subject experiences a bleed while receiving rVWF three times per week, the investigator should treat the bleed with rVWF at doses up to 80 IU VWF:RCo/kg at a frequency determined by the investigator until the bleed resolves. Upon resolution of the bleeding event, the subject will return to their assigned prophylaxis regimen.

It is essential for the success of this study that the subjects adhere to treatment regimens. Therefore, procedures for monitoring subject's compliance are implemented (see Section 10.7).

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. For example, a subject routinely infuses IP on Monday and Thursday, he/she misses the Monday time point and therefore may infuse the IP on the next day (Tuesday) and thereafter proceed with infusing the IP on Thursday (considering a minimum 12 hours between the infusions) and return to the initial schedule.

If more than 30% of infusions of IP are missed within the visit interval of 3 months the subject will be discontinued from the study (see Section 9.4).

8.6.4.3.2 General Instructions for Home Treatment for Prophylaxis

At the discretion of the investigator, a subject may be considered suitable for home treatment only after the subject has received at least 1 infusion of IP in the clinic, either during planned IP exposure (PK or prophylaxis) or during the treatment of bleeding episodes, and meets the following additional criteria:

1. Fully understands the concept of a clinical study and related documentation (documented training of at least 30 minutes),
2. Has a history of previous experience with home treatment including self-administration and treatment with VWF containing concentrates,
3. Has adequate time for initial training of the study drug preparation (preparation, mixing and infusion of the IP(s) (documented training of at least 30 minutes).

In the event a healthcare professional is required to administer IP, he/she must be trained and qualified by the sponsor on the above procedures prior to the decision for home treatment. A Subject Guideline detailing all instructions and information listed above will be provided to each subject.

8.6.4.4 Treatment of Bleeding Episodes

8.6.4.4.1 General Instructions for Home Treatment of Bleeding Episodes

If a subject experiences a bleeding episode, he/she should contact the study site immediately and the site investigator should provide instructions on the treatment regimen. If the subject initiates the treatment at home, he/she should at least follow up with the study site if a visit is needed as per the standard of care at the center.

In the event a healthcare professional is required to administer treatment at the subject's home, he/she must be trained and qualified by the site investigator on the above procedures prior to the decision for home treatment. Once a subject has received 1 infusion of rVWF in the clinic (either during planned IP exposure or during the treatment of a bleeding episode) and meets the criteria for home treatment, the treatment of bleeding episodes with IP can be conducted at home (see Section 8.6.4.3.2).

If a subject is not qualified for home treatment, rVWF infusions must be administered at the study site.

If a subject experiences a bleeding episode that requires treatment between the screening and the prophylaxis initiation visit, the subject will be treated with IP (rVWF with or without ADVATE). Treatment with IP must occur at the study site unless the subject has previously qualified for home treatment with rVWF. If rVWF treatment is not feasible, the subject may use his/her standard of care, such as commercial pdVWF/FVIII products. In any case a washout period of at least 5 days is required prior to rVWF PK infusion at the PK assessment visit.

If a subject experiences a bleeding episode requiring treatment during the PK assessment, rVWF will be used to treat the bleed. Blood draws for PK assessment will be stopped and the PK assessments will be repeated once the bleed has resolved and the subject is free of any symptoms related with the bleeding episode. Dose and frequency of rVWF infusions or any other replacement therapy to stop the bleed should be recorded in the e-CRF.

8.6.4.4.2 Dosing Recommendations for Treatment of Bleeding Episodes

If an acute bleeding episode occurs, the subject will be treated with rVWF with or without ADVATE. In general initially, an infusion of rVWF: ADVATE at an rVWF: ADVATE ratio of 1.3:1± 0.2 will be administered. Subsequent infusions will be with rVWF:RCo 40 to 60 IU/kg with or without 30 to 45 IU/kg ADVATE (only to be administered if plasma FVIII levels fall below 30 IU/L during the treatment period).

If FVIII levels are not available, dosing is at the discretion of the investigator based upon the individual subject's PK data. Using ADVATE in addition to rVWF in subsequent doses carries the risk of an excessive rise in FVIII:C. Therefore, reduced doses of ADVATE and/or prolongation of the dose interval should be considered.

In general the aim of the initial dose should be full replacement of VWF with VWF:RCo levels of >0.6 IU/ml (60%) and FVIII:C of >0.4 IU/mL (40%). In major bleeding episodes, subsequent doses should keep the trough level of VWF:RCo >50% for 3 days and then as deemed necessary by the investigator for subsequent days. In moderate bleeding episodes, the dose and trough level may be reduced to >30% for as long as deemed necessary by the investigator. Treatment for minor bleeding episodes will generally consist of only 1 or 2 doses of rVWF IP.

If the VWF:RCo level is above 150%, a planned treatment should be delayed by at least 12 hours; if the VWF:RCo level is above 200%, a planned treatment should be delayed by at least 24 hours. In either case, a lower subsequent dose (e.g., 20 IU/kg VWF:RCo) may be appropriate.

Dosing recommendations are listed in Table 3.

Dosage must be individualized based on the subject's weight, VWD type, and the severity of the bleeding episode, as well as on monitoring of appropriate clinical and laboratory measures. In the phase 1 study **070701**, 1.0 IU/kg VWF:RCo raised the circulating level of VWF:RCo by 0.017 IU/mL (1.7 %). In the same study, the observed mean half-life for rVWF was 19.3 hours, with a standard deviation of 10.9 hours.

Table 3
rVWF:RCo Dosing Recommendations for the Treatment of Bleeding Episodes Due to VWD

Classification of VWD	Hemorrhage	Dosage (IU VWF:RCo/kg Body Weight)
Type 1 • Severe (Baseline VWF:RCo activity typically <20%)	Minor (e.g., epistaxis, oral bleeding, menorrhagia[a])	40 to 50 IU/kg (1 or 2 doses)
	Major (e.g., severe or refractory epistaxis, menorrhagia*, GI bleeding, CNS trauma, hemarthrosis, or traumatic hemorrhage)	Initial dose 50 to 75 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment
Type 2 (all variants) and Type 3	Minor (clinical indications above)	40 to 50 IU/kg (1 or 2 doses)
	Major (clinical indications above)	Initial dose of 60 to 80 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment

[a] Menorrhagia is defined as excessive bleeding during menstruation. A diagnosis of menorrhagia will be defined by a prospectively completed Pictorial Blood Assessment Chart (PBAC) score >185 and normal cervical cytology or requiring use of a VWF-containing concentrate for treatment of excessive menstrual bleeding for at least one menstrual cycle during the prior year.

Variances of up to 10% in dosing are permissible during treatment of bleeding episodes, but rounding to the nearest vial size should be avoided.

Subjects with non-neutralizing binding anti-VWF antibodies should initially be treated with a dose known to be efficacious based on the subject's medical treatment history which may differ from the recommendations provided in Table 3. Subjects should be monitored for lack of efficacy as well as for FVIII (mandatory), VWF:RCo (mandatory), and VWF:Ag (optional where testing is not available) levels after 3 to 6 hours. Re-dosing with rVWF in combination with ADVATE using the same (initial) dose and adaptation of the dosing frequency should be considered until cessation of the bleed, if the FVIII and/or VWF:RCo levels drop below 30%-50% depending on bleeding severity.

The number of subsequent infusions and the dosage levels prescribed will be determined by the investigator on the basis of the clinical severity, response to current therapy, available laboratory data, and the subject's historical treatment for similar bleeding episodes.

8.6.4.5 Treatment of Surgical Bleeding

Subjects enrolled in this study who require surgery or dental procedures will be treated with investigational product to manage their surgical bleeding then afterwards will resume their prophylactic rVWF treatment schedule.

8.6.4.5.1 Major, Minor and Oral Surgery Definition

The following definitions and criteria are used to serve as a guidance for *major, minor and oral surgery*.

Major surgeries generally refer to major orthopedic surgery (e.g., joint replacement, arthroscopic or open synovectomy, arthrodesis, hardware removals like plates or intramedullary nails, etc.), major abdominal surgery (e.g. open or laparoscopic hernioplasty, cholecystectomy, colon or small bowel resection, etc.), major gynecological surgery (e.g. open or laparoscopic myomectomy, hysterectomy, removal of endometriosis, polyps, cysts, adhesiolysis, etc.), major head and neck surgery (e.g.: tonsillectomy, adenoidectomy, rhinoplasty, lymphadenectomy, thyroidectomy, parotidectomy. etc.), any intracranial , cardiovascular or spinal surgery and any other surgery which has a significant risk of large volume blood loss or blood loss into a confined anatomical space. Extraction of impacted third molars is generally also considered major surgery due to the expected difficulty of surgery and the expected blood loss.

Minor surgeries generally refer to interventions such as placement of intravenous access devices, removal of small skin lesions, arthroscopy, gastroscopy, colonoscopy or conisation.

Oral surgeries comprise extractions of fewer than three teeth, if the teeth are non-molars and have no bony involvement.

A summary schedule of visit assessments and laboratory sampling is included in Supplement tables in Section 20.2.1 and Section 20.3.1.

8.6.4.5.2 Preoperative Priming Dose

12- 24 hours prior to surgery, a priming dose with rVWF, using the rVWF and ADVATE IR and $T_{1/2}$ for this subject , will be infused to allow the endogenous FVIII levels to raise to at least 30 IU/dL (minor, oral surgery), or 60 IU/dL (major surgery) before the loading dose of rVWF is infused.

As a general guidance a priming dose of 40-60 IU/kg rVWF:RCo will be administered.

8.6.4.5.3 Preoperative Loading Dose

An rVWF loading dose should be administed within 3 hours before surgery.

The preoperative loading dose will be calculated as the difference in the target peak and baseline plasma VWF:RCo levels divided by the IR. For minor and oral surgery, the target peak is 50-60 IU/dL VWF:RCo and 40-50 IU/dL FVIII. For major surgery, the target peak is 100IU/dL VWF:RCo and 80-100 IU/dL FVIII.

If FVIII levels prior to loading dose administration are not at least 30 IU/dL (minor, oral surgery), or 60 IU/dL (major surgery) ADVATE will be administered in addition to rVWF in order to raise FVIII:C levels to recommended levels.

The surgery may only start after normalization of the activated partial thromboplastin time (aPTT).

8.6.4.5.4 Intra- and Postoperative (maintenance) Dosing

After the preoperative loading dose(s), subjects who have not achieved the desired postinfusion recovery will continue to receive rVWF with or without ADVATE as a bolus infusion, depending on VWF and FVIII levels. The peri- and postoperative substitution regimen will be individualized according to the PK results, intensity and duration of the hemostatic challenge, and the institution's standard of care.

Subjects undergoing minor surgery will be infused with rVWF every 12-24 hours or every other day, targerting ≥30IU/dL (rVWF and FVIII) for at least the first 48 hours.

Subjects undergoing oral surgery will be infused with rVWF at least once within the first 8-12 hours, targeting ≥30 IU/dL (rVWF and FVIII).

Subjects undergoing major surgery will be infused with rVWF every 12-24 hours for at least the first 72 hours post-surgery, targeting a VWF:RCo and FVIII:C trough plasma level >50 IU/dL, followed by further treatment post-72 hours for as long as deemed necessary by the Investigator, targeting a VWF:RCo and FVIII:C trough plasma level of ≥30 IU/dL.

Dose modifications based on pre-infusion VWF/FVIII levels will be performed as needed. For subsequent infusions post surgery, in case pre-infusion levels are not available prior to the consecutive infusion in a timely manner, pre-infusion levels from the previous dose may be used by the investigator for dosing guidance.

Peak plasma level guidance is matching to Section 8.6.4.4.2

A schedule of all perioperative visit assessments and laboratory sampling can be found in supplement tables in Section 20.2.1 and Section 20.3.1.

8.6.4.6 Thrombosis Prophylaxis

Thromboembolic events have been reported in patients who have VWD, especially in the setting of known risk factors for thrombosis. Hence, in all patients who have VWD and are receiving VWF concentrate, attention should be given to avoid exceeding maximal recommended plasma activity levels of VWF:RCo (250 IU/dL) and FVIII (250 IU/dL), perform proper thrombotic-risk assessment, and institute appropriate preventive strategies.

Anticoagulation measures, such as heparin, are acceptable and should follow study site standards. The investigator will record the use and reasons for such measures/agents on the appropriate CRF.

8.6.5 Investigational Product Accountability

The investigator will ensure that the IP(s) is stored as specified in the Pharmacy Manual and that the storage area is secured, with access limited to authorized study personnel. The investigator will maintain records that the IP(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. The IP(s) must be dispensed only at the study site or other suitable location (e.g., infusion center; home, as applicable per study design), as specified in the protocol (see Section 10). Records will be maintained that includes the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

8.7 Source Data

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

No data will be entered directly onto the CRF.

For additional information on study documentation and CRFs refer to Section 17.2. The use of subject diaries is described in Section 10.5.

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding
   a. Type 1 (VWF:RCo <20 IU/dL) or,
   b. Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2M or,
   c. Type 3 (VWF:Ag ≤3 IU/dL).
2. Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.
3. Subject currently receiving on-demand treatment for whom prophylactic treatment is recommended according to standard of care at the center.
4. Has ≥3 documented spontaneous bleeds requiring VWF treatment during the past 12 months
5. Availability of records to reliably evaluate type, frequency and treatment of bleeding episodes during 12 months of on-demand treatment prior to enrollment.
6. Subject is ≥18 years old at the time of screening and has a body mass index ≥15 but <40 kg/m^2.
7. If female of childbearing potential, subject presents with a negative blood/urine pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.[i]
8. Subject is willing and able to comply with the requirements of the protocol.

9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

1. The subject has been diagnosed with Type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD (eg qualitative and quantitative platelet disorders or elevated PT/INR >1.4).

[i] Refer to Section 20.4 for a list of adequate contraceptive methods for females of childbearing potential.

2. The subject has received prophylaxis treatment in the 12 months prior to screening (including those who received treatment once a month for menorrhagia but were not treated for any other bleeds).
3. The subject is currently receiving prophylaxis treatment.
4. The subject has a history or presence of a VWF inhibitor at screening.
5. The subject has a history or presence of a FVIII inhibitor with a titer ≥0.4 BU (by Nijmegen modified Bethesda assay) or ≥0.6 BU (by Bethesda assay).
6. The subject has a known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins.
7. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
8. The subject has a medical history of a thromboembolic event.
9. The subject is HIV positive with an absolute Helper T cell (CD4) count $<200/mm^3$.
10. The subject has been diagnosed with significant liver disease as evidenced by any of the following: serum ALT 5 times the ULN; hypoalbuminemia; portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).
11. The subject has been diagnosed with renal disease, with a serum creatinine level ≥2.5 mg/dL.
12. The subject has a platelet count <100,000/mL at screening.
13. The subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to signing the informed consent.
14. The subject is pregnant or lactating at the time of enrollment.
15. Patient has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
16. The subject has participated in another clinical study involving another IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
17. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.

18. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
19. The subject has a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
20. The subject is in prison or compulsory detention by regulatory and/or juridical order.
21. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.

9.3 Delay Criteria

1. If the subject has an acute bleeding episode or presents with an acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) the screening visit will be postponed until the subject has recovered.

9.4 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (i.e., reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the termination visit (including cases of withdraw or discontinuation) are described in Section 10.6 and Section 20.2.

Discontinuation (i.e., complete withdrawal from study participation) may be due to dropout (i.e., active discontinuation by subject) or loss to follow-up (i.e., discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also will be withdrawn from treatment or discontinued from further study participation for the following reasons:

1. The subject is scheduled for an extended treatment period >3 months with non-topical immunomodulating drugs other than anti-retroviral chemotherapy (e.g., α-interferon, corticosteroid agents [equivalent to hydrocortisone greater than 10 mg/day]) during the course of the study
2. Subjects with chronic hepatitis B or C develop ALT/AST levels exceeding 5 times the ULN for >1 month

3. Subjects who experience severe hypersensitivity reactions, e.g., anaphylaxis upon exposure to rVWF
4. Subjects who develop a neutralizing inhibitor to rVWF and/or ADVATE (biological assays)
5. Subjects who demonstrate clinical signs of thromboembolic events
6. The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through completion of the pregnancy and up to 1 year post delivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome.
7. The subject begins lactating. IP exposure will be discontinued. The investigator will record a narrative description of the course of the baby's development.
8. The subject is not compliant with the prophylactic treatment regimen and does not adhere to the frequency of IP administration. Once ≥30% of infusions are missed within a visit interval (3 months), the subject will be discontinued from further participation in the study.

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient who provides informed consent (i.e., signs and dates the informed consent form) is considered a subject in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (e.g., 090701) to be provided by the sponsor, 2- or 3-digit number study site number (e.g., 02) to be provided by the sponsor, and 3- or 4-digit subject number (e.g., 0003) reflecting the order of enrollment (i.e., signing the informed consent form). For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 090701-020003. All study documents (e.g., CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The study site is responsible for maintaining a screening log that includes all subjects who provided informed consent. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

The overall study design is illustrated in the Figure 1. Details on the procedures to be performed at each study visit, including screening, are provided in Supplement 20.2 Schedule of Study Procedures and Assessments and Supplement 20.3 Clinical Laboratory Assessments.

10.3.1 Screening Visit

Written informed consent must be obtained from each subject before any study related procedures are performed. To initiate screening procedures, at least 72 hours must have elapsed since the last VWF administration and the subject must not be actively bleeding at the time of screening. Multimer analysis and VWD gene mutation analysis should be performed at screening if not available in the subject's medical history. The screening visit will be delayed if the subjects presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like symptoms, inflammatory diseases) until the event has resolved.

All screening procedures and confirmation of eligibility shall take place within 42 days prior to the first infusion of IP for PK assessments. If the IP is not infused within 42 days, all screening assessments except blood group, human leucocyte antigen (HLA), genetics, multimeric pattern and [redacted], must be repeated to reconfirm eligibility. Refer to Supplement 20.2 and Supplement 20.3. Upon completion of screening procedures, subject eligibility will be confirmed by the sponsor on a subject eligibility form before additional study procedures are undertaken. The subject will maintain a diary that will include infusion logs (see Section 10.5). The allocation of IP will be initiated after the subject has qualified for home treatment (see Section 8.6.4.3.2).

In the event of a subject experiencing a bleeding episode that requires treatment between the screening visit and the baseline visit (PK assessment visit), the subject will be treated with rVWF. If rVWF is not available for any reason, e.g., subject not yet trained on IP administration, study site visit for IP administration not feasible, etc., the subject may use his/her standard of care, such as commercial pdVWF/FVIII products.

10.3.2 Baseline Visit - PK-Assessment Visit

After screening and confirmation of eligibility each subject will undergo a PK assessment. All subjects will receive a dose of 50 ± 5 IU/kg rVWF:RCo to determine VWF and FVIII levels. 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). See Section 20.2 and Section 20.3. IP infusion vials from the same lot number should be used for all PK-assessments per subject. Samples for measurement of FVIII and VWF activity taken through to 6 hours post-infusion will be obtained from an extremity different from that used for the infusion of IP. Where needed, the phlebotomy site will be kept patent via an infusion of normal saline. In this event, at least 5 mL of blood will be collected and discarded before collection of the next test sample into a fresh syringe.

If the subject has a central venous catheter, the central line should be used to administer the infusion and a peripheral venipuncture should be used to collect the blood samples. In the event that a blood sample must be drawn through the central line used for administration of IP, the line must first be flushed with at least 10 mL normal saline or other suitable catheter flush solution that does not contain anticoagulant. At least 5 mL of whole blood must be collected and discarded prior to obtaining the sample.

If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.6.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment.

10.3.3 Prophylaxis Initiation Visit

After the blood sample for the 96 hour PK assessment is drawn the subject will receive the first rVWF prophylactic dose of 50 ± 10 IU/kg rVWF: RCo. Details on dose are provided in Section 8.6.4.3.

Procedures and assessments at this visit include: adverse events, bleeding episodes, medications taken, and non-drug therapies. Independent of previous PK assessment visits, within 2 hours prior the IP infusion, a physical examination will be performed. Vital signs will be assessed within 30 minutes prior to IP rVWF infusion and 30 minutes ± 15 minutes after IP infusion. Further details are provided in Supplement 20.2 and Supplement 20.3.

10.3.4 Treatment of Bleeding Episodes

Treatment of bleeding episodes is described in detail in Section 8.6.4.4 and treatment of perioperative bleeding is described in detail in Section 8.6.4.5.

10.3.5 Perioperative Visits (only applicable is surgery is needed)

The perioperative visits from priming dose through postoperative day 14 will be required to check daily intra- and postoperative weight-adjusted dose of rVWF with or without ADVATE. Details on the procedures and assessments performed at each visit can be found in supplement tables in Section 20.2.1 and Section 20.3.1.

10.3.6 Follow-Up Visits (1 Month ± 1 Week, 2 Months ± 1 Week, 3 Months ± 2 Weeks, 6 Months ± 2 Weeks, 9 Months ± 2 Weeks)

Visits will be performed after the prophylaxis initiation visit at 1 month ± 1 week, 2 months ± 1 week, and 3 months ± 2 weeks and thereafter every three months ± 2 weeks. Additional visits may occur if clinically indicated (see Section 10.3.7).

When possible, site visits should be scheduled on days when the subject is expected to infuse BAX111. Within 2 hours prior to the rVWF IP infusion, a physical examination will be performed. Vital signs will be assessed within 30 minutes prior to IP infusion and 30 minutes ± 15 minutes after IP infusion. Incremental recovery (IR) will be determined at each follow-up visit based on VWF:RCo activity assessed prior to and after IP infusion.

The blood sample for IR analysis will be drawn within 30 minutes prior to IP infusion and 30 minutes ± 5 minutes after IP infusion. rVWF will be infused at the regular prophylactic dose, i.e., 50 ± 10 IU/kg rVWF:RCo. For each subject's recovery analysis IP infusion, vials from the same lot number should be used.

Testing for VWF:RCo VWF:CB, rVWF:Ag, and FVIII:C level will be performed using the blood sample obtained before and after IP infusion.

The blood sample prior to IP infusion will also be used for the assessment of neutralizing and binding antibodies, clinical chemistry and hematology. A washout period of at least 72 hours after the last infusion applies before the blood draw for the immunogenicity assays. Bleeding episodes and the hemostatic efficacy will be evaluated based on the review of the patient diary. See Section 20.2 and Section 20.3. The evaluation of IP consumption and treatment compliance will be performed based on subject's diary entries. If a subject is not compliant with the prophylactic treatment regimen and does not adhere to the required frequency of administration of IP infusions (>30% of infusions were missed within a visit interval [3 months]) the subject will be withdrawn from the study.

At the 6 months ± 2 week visit an electrocardiogram (ECG) will be performed and [redacted] data will be collected.

For the hemostatic efficacy assessment the following information will be recorded by the subject in the patient diary: bleeding location, type, severity, onset and resolution date and time, infusion date and time, clinical efficacy according to the rating scale. If at any time during the study a subject's bleeding episode does not adequately respond to rVWF therapy, he/she will be evaluated for the presence of neutralizing and total binding antibodies. Refer to Section 12.9.3.2.

Further guidance on completing the subject's diary will be provided to the subjects during training for home treatment (see Section 8.6.4.3.2).

10.3.7 Unscheduled Visits

For any unscheduled visit (except for collection of IP) a clinical assessment will be performed as per the scheduled follow-up visits with the exception of [redacted], ECG, and IR determination (refer to Supplement 20.2 and Supplement 20.3).

Subjects who have more than one bleeding episode in 3 months, or an increased frequency of bleeding, should go to the study site for an unscheduled visit.

Follow-up visits after the subject has experienced a bleed may be requested by the investigator. Additional assessments may be required which are at the discretion of the investigator.

10.3.8 Study Termination Visit (12 Months ± 2 Weeks)

At the 12 month ± 2 week visit, a full PK analysis, as per the baseline PK assessment, will be performed. 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). If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.6.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment.

The following parameters will be used as part of the PK assessment:

- Incremental recovery of VWF:RCo, VWF:Ag, and VWF:CB
- AUC/dose, area under moment curve (AUMC/dose, clearance (CL), Volume of distribution at steady state (V_{ss}), mean residence time (MRT), of VWF:RCo ,VWF:Ag, and VWF:CB
- Half-life of VWF:RCo, VWF:Ag, and VWF:CB
- Time course of the FVIII:C levels
- VWF collagen binding (VWF:CB) levels

Refer to Supplement 20.2 and Supplement 20.3 for the other assessments to be performed at the PK assessment and study completion visits.

A washout period of at least 72 hours is required between the PK infusion and the study termination visit (at the time of the 96 hour postinfusion PK assessment).
Refer to Supplement 20.2 and Supplement 20.3 for the list of assessments to be performed at the termination visit.

Subjects will be offered the option to continue to receive BAX111 in a long-term continuation study.

10.4 Medications and Non-Drug Therapies

The following medications and non-drug therapies are **not** permitted within 30 days before study entry and during the course of the study:

Medications:

- 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) and an extended treatment period >3 months.
- Another investigational and/or interventional study drug (except rVWF and FVIII administered under the surgery protocol).

A subject who has taken any of these medications or received any of these non-drug therapies during the study will be withdrawn from the study.

The following medications are permitted during the course of the study:

- Antifibrinolytics (e.g., tranexamic acid, ε-amino caproic acid) or topical hemostats as needed, according to each institution's standard of care
- Emergent use of a VWF concentrate other than rVWF may be permissible under certain circumstances (see Section 8.6.4.4.1)

Details of all adjunctive hemostatic medication used, including dose and reason for use, will be recorded in the electronic Case Report Form (eCRF).

10.5 Subject Diary

1. An electronic subject diary will be provided to each subject at the baseline visit to record the following information:
    - IP infusions to include date, start and stop times of the infusion, number of vials utilized, and infusion volume for prophylactic treatment or treatment of spontaneous and traumatic bleeding episodes
2. Details of bleeding episodes (site and type of bleeding) and response to treatment as described in Section 8.6.4.4
3. Subjective hemostatic efficacy assessments.

Subjects and/or their legally authorized representatives will be trained on use of the diary. The diary will be provided in electronic format and remain with the subject for the duration of the study. The investigator will review the diary for completeness and request missing information periodically and in a timely manner.

Infusions performed at the study site will first be recorded in the site's source documents and not in the patient diary.

Subject entries in the diary will serve as source records. During study participation the investigator has access to the database holding the subject diary data. After study closure, the investigator will receive the diary records for their subjects, including audit trail records, in PDF format. The data will be transmitted to the CRF by a validated transfer.

Paper diary may be utilized in rare case where electronic diary use is not possible.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have completed all study procedures according with the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, AE (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, e.g., technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the study termination visit. If the termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the termination visit. If a subject terminates participation in the study and does not return for termination visit, his/her last recorded assessments shall remain with the last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.2 Schedule of Study Procedures and Assessments and Supplement 20.3 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

10.7 Procedures for Monitoring Subject Compliance

Subject compliance with the procedures of this study (treatment regimens and study visits) will be monitored by the investigator or/a licensed healthcare professional at the study site.

During the regular scheduled follow-up visits a direct review of the subject's source data (e-diaries) will be performed at the sites and evaluated against the protocol requirements. In addition drug accountability will be evaluated at each follow-up study visit and the study termination visit by comparing the infusions recorded in the subject diary with empty vials returned by each subject to the study site, and the study site's dispensing record. Protocol deviations will be noted in the final report.

11. ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

11.1 Assessment of Spontaneous Bleeding Episodes/Annualized Bleed Rate

The annualized bleed rate (ABR) will be assessed based upon each individual spontaneous bleed, requiring coagulation factor replacement therapy, i.e., rVWF treatment. The following details on bleeding episodes will be recorded by the subject in the electronic diary (for home treatment), the subject's healthcare provider in the site's source documents (for treatments away from the primary investigative site), or by authorized, qualified personnel at the participating site in the subject's medical records (for hospital-based treatment):

- Location of bleed; i.e., joint, menorrhagia, epistaxis, gastrointestinal, soft tissue, muscle, body cavity, intracranial, etc.
- Type of bleed; i.e., spontaneous, traumatic, unknown
- Severity of bleed; i.e., minor, moderate, and major (see Table 3)
- Date and time of onset of bleed
- Date and time of each infusion of rVWF or rVWF-ADVATE used to treat a bleeding episode
- Date and time of resolution of the bleeding episode

Study site personnel are qualified after they have undergone training during the qualification of the site.

All types of bleeds, including traumatic bleeds, will be recorded. Bleeding episodes should be organized by where they occur in addition to whether they occurred spontaneously or due to a traumatic event.

Bleeds occurring at the same anatomical location (e.g., right knee) with the same etiology (i.e., spontaneous versus injury) within 24 hours after onset of the first bleed will be considered a single bleed. Bleeding occurring at multiple locations related to the same injury (e.g., knee and ankle bleeds following a fall) will be counted as a single bleeding episode.

All efforts should be made to use rVWF for treatment of bleeding episodes. If needed, the use of a VWF concentrate other than IP for the treatment of bleeding episodes will not disqualify the subject from further participation in the study.

11.2 Evaluation of ABR Before rVWF Prophylaxis and ABR Under rVWF Prophylactic Treatment

At screening, the subject's medical history will be recorded, including the number of all spontaneous and traumatic bleeding episodes within the past 12 months. The maximum interval of bleed-free periods as well as trauma induced bleeding episodes will also be recorded (prospectively and retrospectively).

11.3 Number of Infusions and Total Weight Adjusted Consumption of rVWF and ADVATE

The number of rVWF and ADVATE (in case of bleeding episode treatment) infusions will be logged in the subject diary. Based on these entries the weight adjusted consumption will be calculated per month and per year.

11.4 Assessment of Efficacy for Treatment of Bleeding Episode

Investigators will be asked to assess and record hemostatic efficacy after resolution of each bleeding episode using the 4-scale rating system outlined in Table 4.

Table 4
Efficacy Rating Scale

Rating	Efficacy Rating Criterion	
	Minor and Moderate Bleeding Events	**Major Bleeding Events**
Excellent (=1)	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF containing coagulation factor containing product required	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF containing coagulation factor containing product required
Good (=2)	1-2 infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required	< 1.5 x infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required
Moderate (=3)	3 or more infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required	≥ 1.5 x infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required
None (=4)	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF containing coagulation factor containing product required	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF containing coagulation factor containing product required

11.5 Assessment of Efficacy for Treatment for Surgical Bleeding

For those undergoing surgery, the operating surgeon will be asked to assess and record actual versus predicated blood loss and intraoperative hemostatic efficacy immediately after surgery.

The investigator will be asked to assess and record an overall assessment of hemostatic efficacy 24 hours after the last perioperative rVWF infusion and on Day 7 and Day 14 using the 4-scale rating system described in Table 5.

Table 5
Assessment of Hemostatic Efficacy

Rating	Overall Assessment of Hemostatic Efficacy 24 Hours After the Last Perioperative rVWF Infusion
Excellent (1)	Intra- and post-operative hemostasis achieved with rVWF with or without ADVATE was as good or better than that expected for the type of surgical procedure performed in a hemostatically normal subject
Good (2)	Intra- and post-operative hemostasis achieved with rVWF with or without ADVATE was probably as good as that expected for the type of surgical procedure performed in a hemostatically normal subject
Moderate (3)	Intra- and post-operative hemostasis with rVWF with or without ADVATE was clearly less than optimal for the type of procedure performed but was maintained without the need to change the rVWF concentrate
None (4)	Subject experienced uncontrolled bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of rVWF concentrate

11.6 Pharmacokinetic Assessment

Details on pharmacokinetic assessments are provided in Section 12.9.1.

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

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, whether or not considered causally related to the IP.

12.1.1.1 Serious Adverse Event

An SAE is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
    - Reviewed and confirmed seroconversion for human immunodeficiency virus
      (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)

- Development of neutralizing VWF antibodies
- Development of neutralizing antibodies to FVIII (titer ≥0.4 BU [by Nijmegen- modified Bethesda assay] or ≥0.6 BU [by Bethesda assay])
- Thromboembolic events (e.g., myocardial infarction, stroke, transient ischemic attack [TIA], deep vein thrombosis [DVT] or pulmonary embolism)
- Anaphylaxis (for definition, refer to Section 12.6.2) or severe hypersensitivity reactions

Uncomplicated pregnancies, following maternal or paternal exposure to IP are not considered an (S)AE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE.

12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any suspected adverse reaction to study treatment (i.e., including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following:

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment

Once determined to meet the criteria for a SUSAR, the sponsor will ensure expedited SUSAR reporting in line with the regulatory requirements in participating countries as outlined in the Safety Management Plan.

12.1.1.3 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet the criteria of an SAE.

12.1.1.4 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (e.g., IB, package insert). “Unexpected” also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.1.1.5 Preexisting Disease

Preexisting diseases that are present before entry in to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described on the AE CRF.

12.1.2 Assessment of Adverse Events

For the purposes of this study, the following will not be considered as AEs and will not be included in the analysis of AEs.

- Bleeding episodes are part of the underlying disease and therefore are not AEs; they will be evaluated in the context of efficacy.
  - For non-serious bleeding episodes caused by an injury, the injury would not be reported as an AE, unless it resulted in a medical finding other than a bleeding episode (e.g., abrasion of skin). Therefore, any VWD-related bleeding event (e.g., epistaxis, gastrointestinal bleeding, musculo-skeletal bleeding, menorrhagia) that is non-serious will not be reported as an AE. However, the investigator may decide that the event is an AE if the event also would have occurred in a healthy individual under the same circumstances.
  - For SAEs: Bleeding events that meet seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) should be reported on the SAE eCRF or SAE Report form as an SAE.
- Seroconversion after documented HAV/HBV vaccination prior to or during the study period.

Each AE from the first IP exposure to the study completion date will be described on the AE CRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2

For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution.

If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the protocol-specified dosage (including underdosing /overdosing [<20 IU/kg rVWF:RCo or >100 rVWF:RCo], abuse, and withdrawal, treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after administration of IP will be reported on a Pregnancy Form and followed-up at 1 year post-delivery, if feasible.

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the SAE Form within 24 hours after awareness: no additional reporting on CRFs is necessary.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.

- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, e.g., assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).
- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of IP
  - An alternative etiology is equally or less likely compared to the potential relationship to the IP
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:

- Reappearance of a similar reaction upon re-administration (positive re-challenge)
- Positive results in a drug sensitivity test (skin test, etc.)
- Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid

➢ Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within 5 days after IP infusion, the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

12.1.2.3 Safety Reporting

Adverse events/SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Table 6) and Section 12.1.2.

Adverse Events/SAEs are to be recorded on the AE page of the eCRF. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the investigational product, must be reported immediately (within 24 hours of the study center's first knowledge of the event). All SAEs must be reported via the Electronic Data Capture (EDC) system by completing the relevant eCRF page(s) in English. For instances in which the EDC may become unavailable, SAEs must be reported using the back-up paper SAE report (SAER) form to meet the 24-hour timeline requirement (for contacts and instructions refer to the SAER form). Once the EDC becomes available, the site must enter all SAE data as reported on the back-up paper SAER form on the applicable eCRF pages.

The initial SAE information reported on the applicable eCRF pages (or back-up SAER Form, if applicable) must at least include the following:

1. Protocol Number
2. Subject identification number and demographics (gender, age at onset of event and/or date of birth)
3. Investigational product exposure
4. Medical Term for Event (Diagnosis preferably)

5. Description of the (S)AE, including:
    - Date of onset
    - (S)AE treatment (drug, dose, route of administration)
    - Causal relationship by the Investigator
    - Measures taken (i.e., action taken regarding investigational product in direct relationship to the AE)
6. Seriousness criteria (ie, death, life-threatening, or other criterion)
7. Cause of death
8. Autopsy findings (if available)
9. Name, address, fax number, email, and telephone number of the reporting Investigator (for paper SAER Forms)

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical trial or trials
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor.
In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committees (ECs) and relevant competent authority(s) are notified of the urgent measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (i.e., from the time of signed informed consent up to but not including the first IP exposure) will be described on the SAER. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE.** NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g. reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (e.g., potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) 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. The subject's medical history will also include documented history of on-demand treatment for the past 12 months and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 months.

All medications taken and non-drug therapies received in the 2 weeks prior to study entry and all concomitant medications and non-drug therapies during study will be recorded on the CRFs.

Data on medical history, drug and non-drug therapy history of those subjects who transition from surgery rVWF study will be used from the eCRF of the main studies, will be updated, if applicable, and transcribed into the respective eCRF of the prophy study.

12.6 Physical Examinations

At screening and subsequent study visits (as described in Section 10.3), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 12.1.1.5), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.6.1 Thromboembolic Events

Thromboembolic events are considered a potential risk of rVWF treatment, hence, clinical evidence of thrombosis will be monitored during the study. In the case of clinical signs of any thromboembolic event other than superficial thrombosis, additional diagnostic procedures are required according to each institution's standard of care which may consist of, but are not limited to the following:

- For deep vein thrombosis (DVT): Magnetic Resonance Imaging (MRI), compression ultrasound or impedance plethysmography.
- For pulmonary embolism: ECG, chest radiography, perfusion/scintiscan or MRI.
- For myocardial infarction: ECG, cardiac enzymes, echocardiography
- For stroke: diffusion-weighted magnetic resonance imaging or computed tomography, ABCD scoring, carotid imaging

Results of diagnostic procedures may be forwarded to the sponsor to be reviewed by an independent external expert panel, such as the DMC, if applicable.

12.6.2 Anaphylaxis

The diagnosis of anaphylaxis is highly likely when any of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g, generalized urticaria, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
    b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a. Involvement of the skin or mucosal tissue (e.g., generalized urticaria, pruritus or flushing, swollen lips-tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c. Reduced BP or associated symptoms (hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to a known allergen for that patient (minutes to several hours):
    a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
    b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP

If a subject develops anaphylaxis in the course of the clinical study this needs to be reported as SAE (Section 12.1.1.1). Additional blood draws for Anti-VWF IgE antibody testing will be drawn (Section 12.9.13).

12.7 Vital Signs

Vital signs will be assessed pre and post-infusion at each visit, if not stated otherwise:

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

Vital signs (pulse rate, respiratory rate, and blood pressure) should be recorded within 30 min before and after IP administration. The assessment of vital signs per planned study visit is outlined in Supplement 20.2.

Vital sign values are to be recorded on the physical examination eCRF. For each vital sign value, the investigator will determine whether the value is considered an AE (see definition in Section 12.1). If assessed as an AE, the medical diagnosis (preferably), symptom, or sign, will be recorded on the AE eCRF. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE, should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.8 Electrocardiogram

A standard 12-lead ECG at rest will be performed at screening, at the 6 month follow-up visit and at the study termination visit and evaluated for medical significance by the investigator.

12.9 Clinical Laboratory Parameters

Refer to the Laboratory Manual for information on collection and processing of samples.

In general all laboratory tests will be performed at central laboratories, except the pregnancy and blood group test which will be performed at the local laboratory. In addition, relevant critical safety laboratory tests for complete blood count (CBC), serum chemistry and/or coagulation parameters such as VWF and FVIII activity may also be performed in the local laboratory to ensure that results will be available immediately to the investigator. In principle, results from the central laboratory will be used for data analysis purposes. The assays performed in the central laboratories are specified in the Laboratory Manual. The investigator will supply the sponsor with a list of the normal ranges and units of measurement for the laboratory variables to be determined at the site. Laboratory values such as antibodies to other proteins are not required immediately and will be assessed later during the course of the study.

Abnormal laboratory values deemed clinically significant by the investigator are to be recorded as AEs (see Section 12.1.2).

12.9.1 rVWF and Endogenous FVIII Pharmacokinetics

PK assessments using a dose of 50 IU ± 5 IU/kg rVWF:RCo will be performed at the baseline visit. If the subject is on on-demand treatment and has received VWF replacement therapy a washout period of at least 5 days is required before the infusion of rVWF for PK assessment can be administered.

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 assay.

Endogenous FVIII activity will be measured using the 1-stage clotting assay.

At the 12 month ± 2 week visit, a full PK analysis will also be performed. 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). If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.6.4.4 has to be followed for the treatment of the bleeding episode.

The subject once recovered is eligible to repeat the PK assessment.

The following parameters will be used as part of the PK assessment:

- Incremental recovery of VWF:RCo, VWF:Ag, and VWF:CB)
- AUC/dose, area under moment curve (AUMC/dose, clearance (CL), Volume of distribution at steady state (V_{ss}), mean residence time (MRT), of VWF:RCo ,VWF:Ag, and VWF:CB
- Half-life of VWF:RCo, VWF:Ag, and VWF:CB
- Time course of the FVIII:C levels
- VWF collagen binding (VWF:CB) levels

12.9.2 Hematology and Clinical Chemistry

The hematology panel will consist of CBC [hemoglobin, hematocrit, erythrocytes (ie, red blood cell count [RBC]), and leukocytes (i.e., white blood cell count [WBC])] with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.

The clinical chemistry panel will consist of sodium (Na), potassium (K), chloride (Cl), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), bilirubin (BILI), alkaline phosphatase (AP), blood urea nitrogen (BUN), creatinine (CR), and glucose (Glu).

Blood will be obtained for assessment of hematology and clinical chemistry parameters at screening, during PK-assessment prior to rVWF IP infusion, after 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours post rVWF IP infusion, at all follow-up visits as per schedule (refer to Supplement 20.3 Clinical Laboratory Assessments), i.e., 4 weeks ± 1 week, 8 weeks ± 1 week and every 3 months ± 2 weeks, and at study completion. Hematology and clinical chemistry assessments will be performed on Ethylenediaminetetraacetic acid (EDTA)-anticoagulated whole blood and serum, respectively, at the central laboratory.

12.9.3 Immunology

12.9.3.1 Antibodies to VWF and FVIII

All subjects will be tested for binding and neutralizing antibodies to VWF and FVIII at screening, at baseline PK assessment, at each of the scheduled follow-up visits and at the study completion visit. Testing will be done prior to IP infusion and with at least a 72 hour wash out period since the last IP infusion. If there is any suspicion of inhibitor development (e.g. excessive bleeding) binding and neutralizing antibodies to VWF and FVIII may be tested at the discretion of the investigator.

12.9.3.2 Neutralizing and Total Binding Anti-VWF Antibodies

The assays to establish the presence of neutralizing and total binding anti-VWF antibodies have been established in the absence of international standards and with only limited numbers of positive controls. Therefore, caution is advised in interpreting positive results. In particular, any clinical association, changes in the natural history of the disease, effect of therapy, etc. needs to be taken into account for final judgment. The sponsor's Medical Director should be consulted for additional advice. As part of the AE follow-up, any sample testing positive needs to be confirmed after 2-4 weeks for central laboratory testing. Only confirmed neutralizing anti -VWF antibodies are considered inhibitors (see Section 12.9.3.4). These subjects need to be closely monitored and therapy adjusted accordingly.

12.9.3.3 Binding antibodies to VWF

The presence of total binding anti-VWF antibodies will be determined by an enzyme-linked immunosorbent assay (ELISA) employing polyclonal anti-human Immunoglobulin (Ig) antibodies (IgG, IgM and IgA). For this assay (ELISA), recombinant human VWF will be coated onto a microtiter plate, then incubated with dilutions of the positive control, the negative control or test sample. Antibodies against human VWF that are present in the samples bind to the coated antigen and will be detected with a horseradish peroxidase (HRP)-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a human monoclonal antibody specific for human VWF spiked into the negative control. The negative control for this assay is pooled normal human plasma.

Plasma samples are analyzed for binding antibodies against the specific antigen in two steps. First, the sample is screened for antibodies and the titer of binding antibodies is determined. Second, the specificity of positive antibody results is confirmed.[16]
In brief, all samples are serially diluted (initial dilution 1:20 and further diluted 1:2).

The titer endpoint, defined as the highest dilution that still gives a positive signal above cut off level, is determined in two independent duplicates. The cut off level is established based on background signal level of healthy plasma donors (n=160) and set to include 5% false positives to be as sensitive as possible (95% percentile). The ELISA assay is validated allowing an assay variability of ± 1 titer step. Therefore, differences ≤ 2 titers steps may be due to variability of the ELISA assay. Specificity has to be confirmed in a competition assay when a sample has a titer of 1:80 or higher in the screening assay. Based on the validation criteria samples tested in the screening assay at 1:20 or 1:40 cannot be confirmed in the competition assay. A positive screening value is confirmed if the difference between the titers determined for the subject sample (re-screen) and for the subject sample with pre-incubation (confirmation sample) is > 2 titer steps. Antibody titers of subject samples will only be reported as positive, if the results of the screening and confirmatory analysis fulfill these acceptance criteria. The titer to be reported is always the one determined in the original screening procedure (independent of the result of the re-screening in the confirmation procedure).

A more detailed test procedure will be supplied upon request or pro-actively if a sample tests positive. A treatment related increase of the binding anti-VWF antibodies is expected, if the titer increases by more than 2 titration steps. These subjects need to be closely monitored and therapy adjusted accordingly.

12.9.3.4 Neutralizing Antibodies to VWF

Three functional VWF assays, collagen binding (VWF:CB) assay, Ristocetin cofactor (VWF:RCo) and FVIII binding (VWF:FVIIIB), will be used to test for the presence of neutralizing anti-VWF antibodies. Neutralizing antibodies to VWF:RCo, VWF:CB and VWF:FVIIIB activities will be measured by assays based on the Bethesda assay established for quantitative analysis of FVIII inhibitors (Nijmegen modification of the Bethesda assay).[17] The amount of inhibitor is expressed as Bethesda units (BU) per mL. One BU is thereby defined as the amount of inhibitor that decreases the measured activity in the assays to 50% of that of the negative control samples. The assays were validated using human plasma samples from two type 3 VWD patients with low (1-2 BU/mL) and high (~10 BU/mL) titer inhibitors and plasma samples from non-human primates immunized with human rVWF (>100 BU/mL)

If a subject has a measurable baseline level of VWF activity in the respective assay, it is taken into account in the calculation of the residual activity. However, if baseline levels are too high (>15% VWF:RCo), inhibitors may not be reliably detected.

To exclude false positive results, the detection limit for anti-VWF inhibitors was set to 1 BU/ml for all 3 assays. The rationale for this cut-off value is the relatively high CI of the underlying assays, making determinations at the end of the evaluation range of the Bethesda reference curve uncertain.[18]

A more detailed test procedure may be requested to further characterize the anti-VWF inhibitors, if detected.

12.9.3.5 Binding Antibodies to FVIII

Binding antibodies against FVIII will be analyzed using a proprietary enzyme immunoassay. The testing strategy will be as described for binding anti-VWF antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.3.6 Neutralizing Antibodies (Inhibitors) to FVIII

Neutralizing antibodies (inhibitors) to FVIII will be assessed by the Nijmegen modification of the Bethesda assay in a central laboratory. To verify a FVIII inhibitor, additional testing (such as tests for Lupus anticoagulants) may be initiated. Positive FVIII inhibitor tests will be defined as ≥ 0.4 BU by the Nijmegen-modified Bethesda assay that is confirmed by a second test performed on an independent sample obtained 2-4 weeks following the first test. Only confirmed positive FVIII inhibitor test result will be reported as an SAE.

12.9.4 Antibodies to Other Proteins

Plasma will be assayed for the presence of antibodies against CHO protein (total Ig), murine IgG and human Furin (total Ig) using proprietary enzyme immunoassays. The testing strategy will be as described for binding anti- VWF antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.4.1 Anti-CHO Protein

Total Ig antibodies (IgG, IgA, IgM) against CHO protein will be analyzed. For this assay (ELISA), CHO protein derived from cultures of untransfected cells and propagated under the identical cell culture conditions used for ADVATE production will be coated onto a microtiter plate, then incubated with dilutions of the positive control, negative control or test sample. Antibodies against CHO protein that are present in the samples bind to the coated antigen and will be detected with a horseradish peroxidase (HRP)-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a polyclonal goat anti-CHO protein antibody spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.4.2 Anti-Murine IgG

A commercially available ELISA (Medac, Hamburg, Germany) will be used to detect and to quantify IgG antibodies originating from human plasma that are directed against mouse-IgG (HAMA: human anti- mouse antibodies). Microtiter plates coated with mouse IgG will be incubated with dilutions of the standard, the positive control, the negative control or the test sample. Antibodies against mouse IgG that are present in the samples bind to the coated antigen and form a bridge to a peroxidase coupled mouse IgG antibody that will be used for detection (bridging format of the ELISA assay). The positive control for this assay will be a polyclonal goat anti-murine IgG spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.4.3 Antibodies to Human Furin

Total Ig antibodies (IgG, IgA, IgM) against human Furin will be analyzed. For this assay (ELISA), recombinant human Furin will be coated onto a microtiter plate, then incubated with dilutions of the positive control, the negative control or test sample. Antibodies against human Furin that are present in the samples bind to the coated antigen and will be detected with a horseradish peroxidase (HRP)-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a human monoclonal antibody specific for human Furin spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.5 Viral Serology

The following viral seromarkers will be assessed at screening:

- HIV: anti-HIV 1, HIV 2
- HAV: anti-HAV (IgG and immunoglobulin M [IgM])
- HBV: Hepatitis B surface antigen (HbsAg), anti-Hepatitis B (HB) core, anti-HBs
- HCV: anti-HCV ELISA
- Parvovirus B19: anti-B19V (IgG and IgM)

Virus serology will be established during the screening period. The relevant confirmatory Polymerase Chain Reaction (PCR) testing may be performed from appropriate left-over samples as needed.

12.9.6 Urinalysis (Dipstick)

The urinalysis will include assessments for erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite and pH and will be performed at the central laboratory.

12.9.7 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. The pregnancy test may need to be repeated during the course of study in countries where mandated by national law.

12.9.8 VWD Mutational Analysis, Multimer Analysis and Human Leukocyte Antigen Genotyping

A cell pellet (buffy coat and erythrocytes) will be retained at the screening visit for VWD gene mutational analysis, VWF multimer analysis and HLA genotype determination if the information is not already available in the subject's medical history. Results from multimer analysis (see Section 12.9.10.1) may contribute to VWD gene mutational analysis. The genetic testing will be done, when the subject consents to the genetic testing.

12.9.9 Blood Group Analysis

The blood group needs to be determined during the screening period. If the information is not already available in the subject's medical history, it has to be determined at the local lab.

12.9.10 Additional Laboratory Testing in Case of Thromboembolic Events

rVWF contains ultra large molecular weight (ULMW) multimers because of a lack of exposure to endogenous VWF protease (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) during the manufacturing process. In vitro and in vivo cleavage of these ultralarge molecular fractions by ADAMTS13 and generation of characteristic satellite bands has been extensively demonstrated during nonclinical and clinical development. Nevertheless, the potential elevated risk of thrombosis and/or other thromboembolic complications due to the administration of ultra large molecular VWF multimers in subjects with normal levels of VWF cannot be completely excluded. Therefore VWF multimer analysis will not only be performed routinely at screening but in case of thromboembolic events both VWF multimer analysis as well as ADAMTS13 activity will be determined to assess any relatedness of these occurrences with IP treatment.

12.9.10.1 VWF Multimer Analysis

The VWF multimer pattern will be assessed using low-resolution sodium dodecyl sulfate (SDS)–agarose gel electrophoresis. High-resolution SDS–agarose gel electrophoresis, with agarose concentrations >1.5%, will be used to determine the satellite band structure of VWF. These analyses will employ Western blot with luminescence video imaging.

12.9.10.2 ADAMTS13 Activity

VWF73 was identified as the 73 amino acid minimal region of the VWF A2 domain required for ADAMTS13 cleavage. The cleavage of this substrate will be detected by a commercially available ELISA-based Chromogenic assay (Technoclone Austria): Cleavage of immobilized VWF73 substrate is detected by a HRP-labeled antibody directed against the cleavage site of VWF73. The amount of bound antibody, which is the function of the ADAMTS13 cleavage is detected by a chromogenic substrate.

12.9.11 Soluble P-Selectin (sP-Selectin)

sP-selectin is a cell adhesion molecule (CAM) found in granules in endothelial cells (cells lining blood vessels) and activated platelets. Data for an association between the sP-selectin concentration, thrombotic thrombocytopenic purpura (TTP) and venous thromboembolism (VTE) are limited and the predictive value has not yet established. A commercial ELISA assay will be employed as an exploratory test. sP-selectin will be determined at the Screening visit and used as indicator for an increased thrombotic risk.

12.9.12 D-Dimer

D-dimer will be used as a marker for DVT and disseminated intravascular coagulation (DIC). While a negative result practically rules out thrombosis, a positive result can indicate thrombosis but does not rule out other potential etiologies, including a recent hemorrhage. Its main use, therefore, is to exclude thromboembolic disease where the probability is low. D-Dimer will be measured at the Screening visit and used as indicator for an increased thrombotic risk.

12.9.13 Additional Laboratory Testing in Case of Severe Hypersensitivity Reactions

If a subject develops a severe hypersensitivity reaction in the course of the clinical study, additional blood draws for anti-VWF IgE antibody testing will be drawn. The presence of anti-VWF IgE will be determined by using the ImmunoCAP®, a VWF-specific IgE blood test (Thermo Scientific). The basis of the ImmunoCAP® technology is a cellulose polymer as solid phase in a plastic capsule providing a large surface for protein binding. rVWF as antigen is covalently coupled to the cellulose polymer.

Detection of specific anti-VWF IgE bound to the antigen will be accomplished by a secondary enzyme-labeled anti-human IgE antibody. Testing for binding anti-human VWF IgE antibodies will be done with 0.5 mL plasma. Antibody containing samples will be identified and quantified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.14 Assessment of Laboratory Values

12.9.14.1 Assessment of Abnormal Laboratory Values

For VWF and FVIII laboratory assessments no evaluation of clinical significance is necessary.

Each other laboratory value (except results to determine genetics of the underlying VWD disease and blood group) has to be assessed by the investigator and the assessment will be recorded on the eCRF. The investigator will determine for each abnormal laboratory value whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 12.1) and record the sign, symptom, or medical diagnosis on the AE CRF, is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.5), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, i.e. because it is due to a preexisting disease, due to a lab error, due to variation or due to another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

Any seroconversion result for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V) shall be re-tested.

12.10 [redacted]

12.10.1 [redacted]

[redacted]

[redacted]

12.10.2 [redacted]

[redacted]

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

[redacted]

[redacted]

13. STATISTICS

13.1 Sample Size and Power Calculations

The determination of the sample size for this study is not based on strict statistical considerations. The sample size of a subset of at least 15 subjects with severe VWD, 5 of whom must have Type 3 VWD, is based on the Guideline on the Clinical Investigation of Human Plasma Derived von Willebrand Factor Products (CPMP/BPWG/220/02).[1]

13.2 Datasets and Analysis Cohorts

13.2.1 Safety Analysis Set

The Safety Analysis Set will be composed of all subjects who received any amount of IP, rVWF:ADVATE or rVWF alone.

13.2.2 Full Analysis Dataset

The Full Analysis Set (FAS) will be composed of all subjects with available bleeding data gathered during prophylaxis IP treatment.

13.2.3 Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set will be composed of subjects who are at least 70% compliant regarding required prophylactic infusions. Only subjects who met all study entry criteria and who had no major protocol violations that might impact efficacy assessments will be included in the PP analysis set.

13.2.4 PK Full Analysis Set

The Pharmacokinetic Full Analysis Set (PKFAS) will be composed of all subjects who received the PK infusion and who provided acceptable data for PK analysis. Acceptable PK data will be defined in the Statistical Analysis Plan.

13.2.5 PK Per Protocol Analysis Set

The Pharmacokinetic 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 affecting the PK period of the study as defined in the detailed Statistical Analysis Plan.

13.3 Handling of Missing, Unused, and Spurious Data

13.3.1 General

Statistical techniques will not be used to identify and exclude any observations as outliers from the analyses. If data are considered spurious, e.g. for lack of biological plausibility, it will be documented to include the reason for exclusion and the analyses from which the data were excluded.

13.3.2 Other

1. Regarding missing data in PK records:
    - Body weight: If a subject's weight is missing from the PK infusion record, the subject's last recorded weight will be used to calculate the weight-adjusted dose.
    - Concentration:
        - Baseline concentration levels reported as below the limit of quantification will be considered to be 0. Missing VWF baseline concentration levels (VWF: RCo, VWF: AG or VWF: CB) for Type 3 subjects will be set to 0.
    - Time:
        - If start time of infusion is missing (but stop time is available) and actual collection time is available, then stop time of infusion will be taken for further calculation (i.e. time difference between actual end date/time of infusion and date/time blood sample drawn).
        - If actual collection date/time is missing and planned collection date/time is missing, then this PK time point will be taken out from the PK analysis (i.e. no data entry for this time point).
        - For all other scenarios, the planned collection date/time will be taken for further calculation.
2. Regarding missing data in AE records:
    - Handling of unknown causality assessment:
        - If a subject experiences an AE with a missing causality assessment, the relationship of the AE will be counted as "related."

- Handling of unknown severity grades:
  - If a subject experiences more than one AE categorized under the same preferred term, 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.

13.4 Methods of Analysis

The study success criteria are the objectives as stated in Section 7. “Treatment success” was defined as the extent of control of bleeding episodes achieved during this study.

13.4.1 Primary Outcome Measure

The statistical analysis will provide descriptive summaries.

For the number of infusions and for the total weight adjusted consumption of rVWF and ADVATE per month and per year during on-demand treatment, summary statistics will be carried out.

For the number (proportion) of subjects with reduction of ABR relative to historic ABR as well as for the number (proportion) of subjects with 0 bleeds, proportions and corresponding 95% two-sided CIs will be performed.

The annualized rate of bleeding episodes will be calculated as (Number of bleeding episodes/observed treatment period in days) * 365.25.

The primary efficacy analysis will be based on the FAS. As a supportive analysis, the same analysis will also be carried out on the PP.

The two time periods (prior to prophylaxis treatment and while on prophylaxis) will be compared within each subject in terms of mean ABR using a generalized estimating equations model framework (with a logarithmic link function which was the default for the negative binomial distribution), accounting for the fixed effect of the two time periods. The follow-up time (in years) will be specified as an offset and an unstructured working correlation matrix will be used to account for the correlated data. Ratios between the two time period means (95% CI) will be estimated within this model by SAS procedure GENMOD.

13.4.2 Secondary Outcome Measures

13.4.2.1 Efficacy

For the number of infusions and for the total weight adjusted consumption of rVWF and ADVATE per month and per year during prophylactic treatment as well as during on-demand treatment for bleeding episodes, summary statistics will be carried out.

For the number (proportion) of subjects with reduction of ABR relative to historic ABR as well as for the number (proportion) of subjects with 0 bleeds, proportions and corresponding 95% two-sided CIs will be performed. An ABR reduction of >25% is considered relevant.

The cause, type, localization and severity of bleeding episodes will also be recorded and summarized. Bleeding episodes should be organized by where they occur in addition to whether they occurred spontaneously or due to a traumatic event.

The secondary efficacy analysis will be performed on the FAS only.

13.4.2.2 Efficacy of the Treatment of Bleeding Episodes

For the number of infusions of rVWF and ADVATE per bleeding episode, for the weight adjusted consumption of rVWF and ADVATE per bleeding event as well as for the overall hemostatic efficacy rating at resolution of bleed, summary statistics will be carried out.

The severity and localization of bleeding episodes will also be recorded and summarized.

The analysis will be performed on the FAS.

13.4.2.3 Efficacy of the Treatment of Peroperative Bleeding Management, if Surgery is Required

Descriptive statistics will be performed for the following secondary outcome measures -

- Intraoperative actual versus predicted blood loss (assessed by the operating surgeon) at completion of surgery
- Intraoperative hemostatic efficacy score on a scale of excellent, good, moderate or none (assessed by the operating surgeon) at completion of surgery
- For elective surgery: an overall assessment of hemostatic efficacy 24 hours after the last perioperative infusion of rVWF, assessed by the Investigator
- Daily intra- and postoperative weight-adjusted dose of rVWF with or without ADVATE through postoperative day 14

13.4.2.4 Pharmacokinetic Analysis

All PK analyses will use the actual sampling times, not nominal times specified in the protocol, wherever possible. Actual sampling times will be defined as time from the start of infusion to the blood sample collection time. A deviation from the protocol-specified blood sample 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 results were biologically implausible will be eliminated from the analysis.

If any concentration data are considered spurious (e.g. lack of biological plausibility), the reason for exclusion from the analysis and the analysis from which the data point was excluded will be documented.

To ensure that values at baseline (pre-infusion) are not affecting the estimation of PK parameters, post-infusion concentration data will be adjusted for baseline as follows:

$$C_{Corrected,\ t} = \left(1 - \frac{C_{Measured,\ pre-infusion}}{C_{Measured,\ Tmax}}\right) \cdot C_{Measured,\ t}$$

After adjustment of the post-infusion concentration data, any pre-infusion data will be set to 0.

$C_{Corrected}$ will be set to missing, if:

- Samples have an unknown draw time or where the concentration could not be determined, or where results were deemed to be unreliable due to analytical issues.
- Any concentration data are considered spurious (e.g. lack of biological plausibility).

Handling of concentrations that are below the quantification limit:

- Baseline concentration values reported as below the limit of quantification will be considered to be 0 ($\rightarrow C_{Corrected}$ = Concentration value)
- Post-infusion concentration values reported as below the limit of quantification or missing repeated concentration values will be set to missing ($\rightarrow C_{Corrected}$ = missing)

The area under the plasma concentration/time curve from time 0 to infinity ($AUC_{0-\infty}$) and the area under the first moment curve from time 0 to infinity ($AUMC_{0-\infty}$) will be calculated as the sum of AUC or AUMC from time 0 to the time of last quantifiable concentration plus a tail area correction calculated as C_t/λ_z and $C_t/\lambda_z(t + 1/\lambda_z)$, respectively, where C_t is the last quantifiable concentration, t is the time of last quantifiable concentration and λ_z is the terminal or disposition rate constant.

The area under the plasma concentration/time curve from time 0 to 72 hours post-infusion (AUC_{0-72h}) will be computed using the linear trapezoidal rule. For the calculation of AUC_{0-72h} the levels at 72 hours will be linearly interpolated/ extrapolated from the 2 nearest sampling time points.

Elimination phase half-life (HL) in hours will be calculated as:

$$T_{1/2} = log_e(2)/\lambda_z$$

where the elimination rate constant (λ_z) will be obtained by log_e-linear fitting using least squares deviations to at least the last 3 quantifiable concentrations above pre-infusion level.

The **Mean Residence Time** (MRT) in hours will be calculated as total area under the moment curve divided by the total area under the curve:

$$MRT = \frac{AUMC_{0-\infty}[h^2 * IU/dL]}{AUC_{0-\infty}[h * IU/dL]}$$

Systemic clearance in dL/kg/h will be calculated as the dose in IU/kg divided by the total AUC:

$$CL = \frac{Dose[IU/kg]}{AUC_{0-\infty}[h * IU/dL]}$$

Apparent **steady state volume of distribution** (Vss) in dL/kg will be calculated as:

$$Vss = \frac{Dose[IU/kg] \times AUMC_{0-\infty}[h^2 * IU/dL]}{AUC^2_{0-\infty}[h^2 * IU^2/dL^2]}$$

The **maximum concentration**, C_{max}, will be calculated as the maximum concentration post-infusion.

The **time to reach the maximum concentration**, T_{max}, in hours was defined as the time to reach C_{max}.

Incremental recovery (IR) in (IU/dL)/(IU VWF:RCo/kg) will be calculated as:

$$IR = \frac{C_{max}[IU/dL] - C_{pre-infusion}[IU/dL]}{dose\ per\ kg\ body\ weight\ [IU/kg]}$$

where C_{max} and $C_{pre\text{-}infusion}$ are the unadjusted concentration values.

The PK parameters $AUC_{0\text{-}72h}$/Dose, $AUC_{0\text{-}\infty}$/Dose, $AUMC_{0\text{-}\infty}$/Dose, MRT (mean residence time), CL (clearance), IR (incremental recovery), $T_{1/2}$ (elimination phase half-life), Vss (Volume of distribution at steady state), C_{max} (maximum concentration) and T_{max} (time to reach the maximum concentration) will be summarized by mean, standard deviation and the corresponding 90% CIs, median, Q1, Q3, IQR and range.

Descriptive statistics will be used to summarize VWF:RCo levels for each nominal time point on the PK curve.

PK analysis as described above will be carried out on the PKFAS as well as on the PKPPAS.

For all subjects in the PKFAS concentration vs. time curves will be prepared.

PK parameters will be derived using non-compartmental methods in WinNonlin.

The analysis will be performed on the FAS.

13.4.2.5 Safety

AEs that occurred during or within 24 hours after first IP infusion will be presented in summary tables. Summary tables shall indicate the number of subjects who experienced adverse events. Separate tables will be carried out for temporally associated adverse events; and for temporally associated or causally related adverse events.

In addition, tables will be prepared to list each AE, the number of subjects who experienced an AE at least once, and the rate of subjects with AE(s). AEs will be grouped by system organ class. Each event will then be divided into defined severity grades (mild, moderate, severe). The tables will also divide the AEs into those considered related (a "possibly related" or a "probably related" AE will be considered as a "related AE") to the treatment and those considered unrelated (an "unlikely related" or a "not related" AE will be considered as an "unrelated" AE). These tables will also be carried out for temporally associated adverse events; and for temporally associated or causally related adverse events.

All AEs; temporally associated AEs; causally related AEs (by investigator assessment); and temporally associated or causally related AEs will also be summarized by system organ class, preferred term, including the number of AEs, the number (%) of unique subjects, the frequency category (very common: ≥10%, common: ≥1% to <10%, uncommon: ≥0.1% to <1%, rare: ≥0.01% to <0.1%, very rare: <0.01%) and the number of IP-infusions associated with an AE.

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 infusion, irrespective of being related or not related to treatment.

AEs and SAEs for each subject, including the same event on several occasions, will be listed separately, giving both MedDRA preferred term and the original verbatim term used by the investigator, system organ class, severity grade, seriousness, relation to the treatment (by investigator assessment; for SAEs this will be by investigator and sponsor assessment), onset date, and stop date.

AEs that occurred before first IP infusion will be listed separately.

Incidences of thromboembolic events and hypersensitivity reactions will be tabulated and also listed per subject. For the development of antibodies, proportions will be carried out.

The safety analyses will be based on the safety analysis set.

13.5 Exploratory Outcome Measures

[redacted]

[redacted]

13.6 Planned Interim Analysis of the Study

No formal interim analysis is planned for this study. However, a descriptive summary report for this study is planned after all subjects have completed at least 6 months of prophylactic treatment with rVWF.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Trial Agreement (CTA). If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the CTA.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable national and local regulatory requirements as described in the CTA. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

15.1.1 Investigator Report and Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the CTA. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the CTA. Auditing processes specific to the study will be described in the audit plan.

15.5 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor (Baxalta) will also ensure the responsible EC and relevant competent authority are notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.6 Laboratory and Reader Standardization

A central laboratory/reader will be used for all clinical assessments except for pregnancy testing and blood group test (refer to Section 12.9). Local laboratories are requested to provide their laboratory specifications of the individual tests that are also being tested locally.

16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the CTA.

16.2 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the CTA.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

16.3 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients and/or their legally authorized representative must sign an informed consent form before entering into the study according to applicable national and local regulatory requirements and ICH GCP. Before use, the informed consent form will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 16.2). The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable national and local regulatory requirements. Patients or their legally-authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent form, patients or their legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised informed consent form, which have been approved by the applicable EC and regulatory authorities, will be provided by the investigator to the subjects who consented to participate in the study

16.4 Data Monitoring Committee

This study will be monitored by Data Monitoring Committee (DMC). The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. 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 stop a trial if it finds toxicities or if treatment is proven to be not beneficial. Details will be defined in the DMC charter.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the CTA.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.7), records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, CRFs, SAERs, laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

If electronic format CRFs are provided by the sponsor, only authorized study site personnel will record or change data on the CRFs. If data is not entered on the CRFs during the study visit the data will be recorded on paper and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (e.g., ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the CTA.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the CTA.

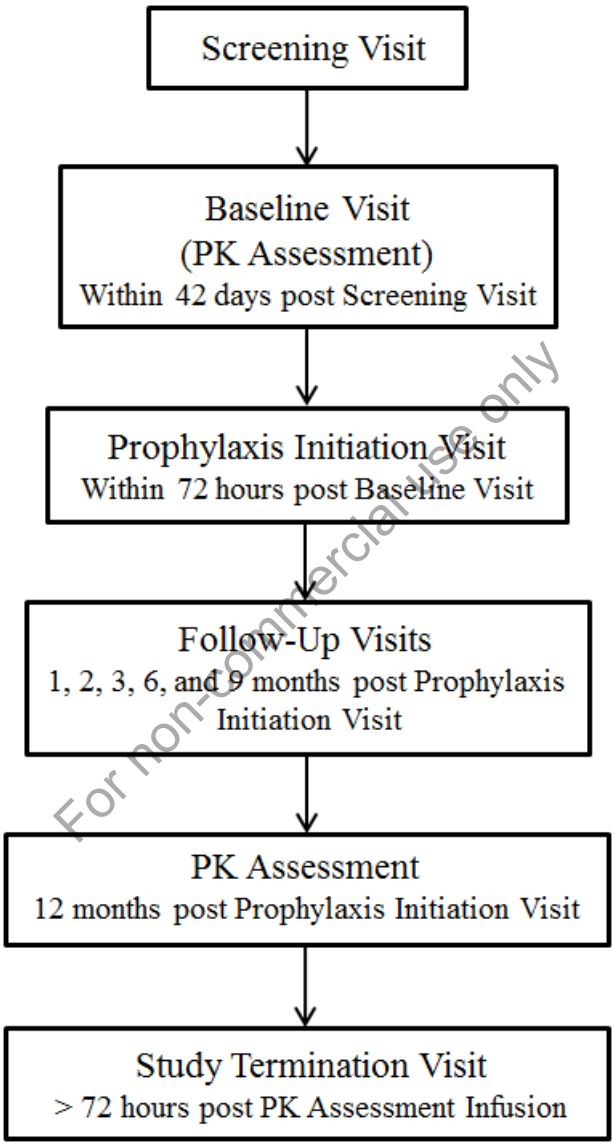
19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the CTA.

20. SUPPLEMENTS

20.1 Study Flow Chart

Figure 1
Study Design for Baxalta Clinical Study 071301



20.2 Schedule of Study Procedures and Assessments

Table 6
Schedule of Study Procedures and Assessments

Procedures/ Assessments	Screening Visit	Baseline Visit (PK-assessment visit)			Prophylaxis Initiation Visit	Interval/Follow-Up Study Visits					PK Assessment and Study Completion			Termination Visit
		Pre-infusion	Infusion	Post-infusion[g]		1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion	Infusion	Post-infusion[g]	Conducted at the 96 hour postinfusion PK Assessment
											12 month± 2 weeks			
Informed Consent [a]	X													
Eligibility Criteria	X													
Medical History[b]	X	X												
Medications[c]	X	X			X	X	X	X	X	X	X			X
Non-drug Therapies[c]	X	X			X	X	X	X	X	X	X			X
Physical Exam	X	X			X	X	X	X	X	X	X			X
Adverse Events		X			X	X	X	X	X	X	X			X
Bleeding Episodes	X	X			X	X	X	X	X	X	X			X
Laboratories	X	X		X	X[h]	X	X	X	X	X	X		X	X
Vital Signs[d]	X	X		X	X	X	X	X	X	X	X		X	X
ECG	X								X					X
IP Treatment[e]			X		X	X	X	X	X	X		X		
IP Consumption / Treatment Compliance						X	X	X	X	X				
Subject Diary					X	X	X	X	X	X				
[redacted]	X[f]								X					X

Continued on next page

Continued

[a]) Occurs at enrollment (before screening).
[b]) Including documented history of on-demand treatment for the past 12 months and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 months.
[c]) Including all medications and non- drug therapies taken in the 2 weeks prior to study entry and all the concomitant medications and non-drug therapies during the course of the study.
[d]) Vital signs (pulse rate, respiratory rate, and blood pressure): within 30 minutes before infusion start and 30 ± 15 minutes post-infusion.
[e]) IP treatment after the prophylactic treatment initiation visit at the site will be continued as home-treatment if the subject qualifies; a wash-out period of at least 72 hours is required after the last IP infusion before the follow-up visit. IP infusion will be given at the study site after the blood sample for immunology testing and IR determination is drawn.
[f]) Can be done either at the screening or the baseline visit.
[g]) Time points for blood draws 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.
[h]) If a subject did not undergo PK assessment, laboratory assessments will be performed at this visit.

20.2.1 Summary Schedule of Visit Assesments for Surgical Bleeding

Table 7
Summary Schedule of Visit Assesments for Surgical Bleeding

Procedures/ Assessments	**Surgical procedure**				**Post-Operative Day 7 Visit (± 1 day)**	**Study Completion Visit (14 ± 2 days post Surgery)**
	Priming Dose Procedures (12-24 hours prior to surgery)	**Loading Dose Procedures (≤ 3 hours prior to surgery)**	**Intraoperative**	**Postoperative (day 1 → end of perioperative IP treatment)**		
ECG						X
Physical examination	X	X		X	X	X
Adverse events	X	X	X	X	X	X
Laboratories	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
IP treatment: rVWF:ADVATE or rVWF only infusion	X	X	X as required	X as required	X as required	X as required
Concomitant medications and non-drug therapy	X	X	X	X	X	X
[redacted]						X
Hemostatic efficacy assessments				X	X	X
Blood loss		X estimated	X actual	X	X	X
Treatment days estimate		X				

20.3 Clinical Laboratory Assessments

Table 8
Clinical Laboratory Assessments

Procedures/ Assessments	Screening Visit	Baseline Visit (PK-assessment visit)			Prophylaxis Initiation Visit[k]	Interval/Follow-Up Study Visits					PK Assessment and Study Completion			Termination Visit
		Pre-infusion	Infusion	Post-infusion[g]		1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion	Infusion	Post-infusion[g]	Conducted at the 96 hour postinfusion PK Assessment
											12 month± 2 weeks			
Hematology [a]	X	X		X	X	X	X	X	X	X	X[m]		X	
Clinical Chemistry[b]	X	X		X	X	X	X	X	X	X	X		X	
Coagulation Panel/PK assessment[c]	X	X		X	X	X	X	X	X	X	X		X	
Immunogenicity[d]	X	X			X[l]	X	X	X	X	X	X		X	
Viral Serology[e]	X													
Urinalysis[f]	X													
VWD Gene Mutational Analysis / HLA genotype analysis and Analysis of VWF multimers[g]	X													
sP-selectin and D-dimer	X[h]													
Blood Group[i]	X													
Pregnancy Test[j]	X													

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Continued

[a)] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. Hematology assessments during PK assessments will be determined prior IP infusion and 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours thereafter.

[b)] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin. Clinical chemistry will be determined at baseline, after 24 ± 2 h, 48 ± 2 hours and 72 ± 2 hours during the PK assessments.

[c)] Coagulation panel/PK assessment (also refers to IR pre/post dose assessments at each follow-up visit): INR/aPTT, VWF:RCo, VWF:Ag, VWF:CB, FVIII:C,; during the PK assessment at the baseline visit blood samples will be drawn 30 min prior PK infusion; once the PK infusion is completed 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 and VWF:RCo, VWF:CB, VWF:Ag, FVIII:C will be determined; in case of thromboembolic event VWF multimers and ADAMTS13 will be analyzed to judge on a possibly relatedness to UHMW fractions of the IP.

[d)] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII – Neutralizing and Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG; .CD4* In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined. A washout period of at least 72 hours after the last IP infusion is required before blood samples for immunogenicity assessments can be drawn.

[e)] Viral Serology 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; HIV-1/HIV-2 Antibodies

[f)] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH

[g)] Not required if available in the subject's medical history; VWF multimers: additionally in case of thromboembolic events

[h)] At screening and in case of thromboembolic events

[i)] Blood group assessment major blood group (local laboratory) only if not available in the subject's medical history

[j)] Serum pregnancy test (in females of child-bearing potential if no urine sample is available)

[k)] The 96 h post-infusion laboratory assessments coincidence with the initiation visit for prophylactic treatment. After the blood samples are drawn for laboratory assessment for the 96 h post infusion PK assessment, the subject receives the first IP infusion for prophylactic treatment (prophylactic treatment initiation visit).

[l)] Only needed for subjects without PK assessment prior to their first IP infusion in this study.

[m)] A full PK analysis will be performed. 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).

20.3.1 Laboratory Sampling for Surgical Bleeding

Table 9
Laboratory Sampling for Surgical Bleeding

Procedures/ Assessments	**Surgical procedure**				**Post-Operative Day 7 Visit (± 1 day)**	**Study Completion Visit (14 ± 2 days post Surgery)**
	Priming Dose Procedures (12-24 hours prior to surgery)	**Loading Dose Procedures (≤ 3 hours prior to surgery)**	**Intraoperative**	**Postoperative (day 1 → end of perioperative IP treatment)**		
Pregnancy Test						
Hematology	X (w/o Differential)	X (w/o Differential)		X (w/o Differential)	X	X
Clinical Chemistry	X	X			X	X
Coagulation panel	X	X	X	X	X	X
Pharmacokinetic Tests						
VWF inhibitory and binding antibodies, antibodies to other proteins	X	X	X if excessive or unexplainedbleeding	X	X	X
Viral markers						
VWD Gene Mutational Analysis / HLA genotype analysis						
Urinalysis					X	X
VWF Multimers						
Anti VWF IgE antibody testing only in case of allergic reaction/ anaphylaxis						

20.4 Contraceptive Methods for Female Subjects of Childbearing Potential

In this study, subjects who are women of childbearing potential must agree to utilize a highly effective contraceptive measure throughout the course of the study and for 30 days after the last administration of investigational product. In accordance with the Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials (version 2014-09-15),[ii] birth control methods which may be considered as highly effective include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable[iii]
- Intrauterine device (IUD)[iii]
- Intrauterine hormone-releasing system (IUS) [iii]
- Bilateral tubal occlusion[iii]
- Vasectomised partner(s)[iii]
- Sexual abstinence during the entire study period

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

[ii] Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf.

[iii] Contraception methods that are considered to have low user dependency.

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22. SUMMARY OF CHANGES

Protocol 071301: Global Amendment 3: 2017AUG 03

Replaces: Amendment 2: 2016 DEC 15

In this section, changes from the previous version of the Protocol, dated 2016 DEC 15, are described and their rationale is given.

1. Synopsis(Secondary objectives, Efficacy), Section 7.3, Section 8.4.2.5, Section 13.4.2.3
   Description of Change:
   The text/summary text/bullets for 'efficacy of treatment of perioperative bleeding management, if surgery is required' is added.
   Purpose for Change: To provide further clarifications to the surgery arm and to address the possibility for subjects on year long prophy study who coud require surgical procedure during this time.

2. Synopsis (Secondary Outcome Measures, Efficacy), Section 8.4.2.1
   Description of Change:
   Original text:
   Number (proportion) of subjects with reduction of ABR for spontaneous (not related to trauma) bleeding episodes during prophylaxis relative to the subjects' own historical ABR during on-demand treatment
   New text:
   Number (proportion) of subjects with reduction of ABR for spontaneous (not related to trauma) bleeding episodes during prophylaxis relative to the subjects' own historical ABR during on-demand treatment. **An ABR reduction of >25% is considered relevant.**
   Purpose for Change: To define the threshold considered as relevant ABR reduction relative to subjects' historical ABR, to improve the clarity of the protocol.

3. Synopsis, Abbreviation list, Section 8.4.2.3, Section 10.3.6, Section 10.3.8, Section 12.9.1, Section 12.9.14, Section 20.3 Table 7 and Footnote "c")
   Description of Change:
   The mention of the 'Innovance VWF Ac assay' is removed from the protocol text.
   Purpose for Change: As the text related to 'Innovance VWF Ac assay' was not applicable for the study, the relevant instances are removed for further clarity.

4. Section 8.4.2.1
   Description of Change:
   Original text:
   Number of infusions and total weight adjusted consumption of rVWF and ADVATE per month and per year during on-demand treatment
   New text:
   Number of infusions and total weight adjusted consumption of rVWF and ADVATE per month and per year **during prophylactic treatment as well as** during on-demand treatment
   Purpose for Change: Calculation of consumption will be carried out on prophylaxis as well as for on demand treatment, so the revision done to improve the clarity of the protocol.

5. Section 8.7.4.1, Section 10.3.2, Section 10.3.7, Section 12.9.1
   Description of Change:
   Original text:
   Blood samples will be drawn within 30 minutes pre-infusion, and at 7 time points post-infusion (30 ± 5 minutes, 60 ± 5 minutes, 6 ± 1 hours, 12 ± 1 hours, 24 ± 2 hours, 48 ± 2 hours, 72 ± 2 hours)
   New text:
   Blood samples will be drawn within 30 minutes pre-infusion, and at ~~7~~**11** time points post-infusion (**15 ± 5 minutes,** 30 ± 5 minutes, 60 ± 5 minutes, **3 ± 0.5 hours,** 6 ± ~~10~~**0.5** hours, 12 ± ~~10~~**0.5** hours, 24 ± ~~10~~**0.5** hours, **30 ± 2 hours,** 48 ± 2 hours, 72 ± 2 hours **and 96 ± 2 hours**)
   Purpose for Change: Need to align with (CPMP/BPWG/220/02) to include 15 min, 3 hr and 30 hr PK sampling timepoints.

6. Section 8.7.4.1, Section 8.7.4.2, Section 10.3.2, Section 10.3.3, Section 20.2 – Footnote "h")
   Description of Change:
   The text related to PK assessments in the subjects previously enrolled in rVWF studies is modified as applicable.
   Purpose of Change:
   Text modified for relevance and further clarification.

7. Section 8.7.4.2, Section 10.3.3, Section 10.3.7, Section 20.3 – Footnote" k")
Description of Change:
All instances of 72 ± 2 hours PK assessment is replaced with 96 ± 2 hour PK assessment, when referring to the case window.
Purpose of Change:
The time point 96 ± 2 hour is the new time span for PK assessment, when referring to the case window.

8. Section 8.7.4.3
Description of Change:
Original text:
rVWF Dosing Schedule Examples: Schedules, A, B, and C
New text:
rVWF Dosing Schedule Examples: Schedules A~~,~~ **and B,** ~~and C~~
Purpose for Change: Table heading corrected to remove error.

9. Section 8.7.4.4.2
Description of Change:
Original text:
If an acute bleeding episode occurs, the subject will be treated with rVWF with or without ADVATE. In general initially, an infusion of rVWF: ADVATE at an rVWF: ADVATE ratio of 1.3:1± 0.2 will be administered. Subsequent infusions may either use rVWF alone or with ADVATE, based on FVIII levels, if available.
New text:
If an acute bleeding episode occurs, the subject will be treated with rVWF with or without ADVATE. In general initially, an infusion of rVWF: ADVATE at an rVWF: ADVATE ratio of 1.3:1± 0.2 will be administered. Subsequent infusions ~~may either use rVWF alone or with ADVATE, based on FVIII levels, if available~~**will be with rVWF:RCo 40 to 60 IU/kg with or without 30 to 45 IU/kg ADVATE (only to be administered if plasma FVIII levels fall below 30 IU/L during the treatment period)**.
Purpose for Change: To clearly define the ADVATE use, the revision of text was done.

10. Section 8.7.4.5
Description of Change: New section added: "Treatment of Surgical Bleeding"
Purpose for Change: Section added in order to address the possibility for subjects on year-long prophy study who could require surgical procedure during this time.

11. Section 8.7.4.6
    Description of Change: New section added: "Thrombosis Prophylaxis"
    Purpose for Change: Section added in order to address the clarity around the thrombosis prophylaxis.

12. Section 10.3.4
    Description of Change:
    Original text:
    Treatment of bleeding episodes is described in detail in Section 8.7.4.4.
    New text:
    Treatment of bleeding episodes is described in detail in Section 8.7.4.4 **and treatment of perioperative bleeding is described in detail in Section 8.7.4.5**.
    Purpose of Change: The reference to new section 8.7.4.5 also added for further clarification, to address this possibility for subjects on year-long prophy study who could require surgical procedure during this time.

13. Section 10.3.5
    Description of Change:
    The details for surgery related Perioperative visit added in new subsection.
    Purpose of Change: The details for surgery related visit added for further clarification, to address this possibility for subjects on year-long prophy study who could require surgical procedure during this time.

14. Section 10.5
    Description of Change:
    Original text:
    Infusions performed at the study site will be recorded in the site's source documents and not in the patient diary.
    New text:
    Infusions performed at the study site will **first** be recorded in the site's source documents and not in the patient diary.
    Purpose of Change: For further clarification, as afterwards site infusions need to be sent to ERT for entry.

15. Section 10.5
    Description of Change:
    Original text:
    Not applicable
    New text:
    Paper diary may be utilized in rare case where electronic diary use is not possible.
    Purpose of Change: New text is added to further clarify that recruitment / retention materials include a paper diary in case needed, so to match to subject-facing material submitted.

16. Section 11.5
    Description of Change:
    Original text:
    Not applicable
    New text:
    New subsection for 'Assessment of Efficacy for Treatment for Surgical Bleeding' is added.
    Purpose of Change: For further clarification, to address this possibility for subjects on year-long prophy study who could require surgical procedure during this time.

17. Synopsis, Section 13.4.2.1
    Description of Change:
    Original text:
    For the number (proportion) of subjects with reduction of ABR relative to historic ABR as well as for the number (proportion) of subjects with 0 bleeds, proportions and corresponding 95% two-sided CIs will be performed.
    New text:
    For the number (proportion) of subjects with reduction of ABR relative to historic ABR as well as for the number (proportion) of subjects with 0 bleeds, proportions and corresponding 95% two-sided CIs will be performed. **An ABR reduction of >25% is considered relevant.**
    Purpose for Change: To define the threshold considered as relevant ABR reduction relative to subjects' historical ABR, to improve the clarity of the protocol.

18. Synopsis, Section 13.4.2.1
    Description of Change:
    Original text:
    For the number of infusions and for the total weight adjusted consumption of rVWF and ADVATE per month and per year during on-demand treatment for bleeding episodes, summary statistics will be carried out.
    New text:
    For the number of infusions and for the total weight adjusted consumption of rVWF and ADVATE per month and per year **during prophylactic treatment as well as** during on-demand treatment for bleeding episodes, summary statistics will be carried out.
    Purpose for Change: Calculation of consumption will be carried out on prophylaxis as well as for on demand treatment, so the revision done to improve the clarity of the protocol.

19. Section 20.2 - Table 6
    Description of Change: Removal of Medical History 'X' in PK assessment and study completion/pre-infusion column
    Purpose of Change: To correct error on study procedure and assessment chart.

20. Section 20.2 – Table 6
    Description of Change:
    Original text:
    Footnote g) Time points for blood draws post infusion: 30 ± 5 minutes, 60 ± 5 minutes, 6 ± 1 hours, 12 ± 1 hours, 24 ± 2 hours, 48 ± 2 hours, 72 ± 2 hours
    New text:
    Footnote g) Time points for blood draws post infusion: **15 ± 5 minutes,** 30 ± 5 minutes, 60 ± 5 minutes, **3 ± 0.5 hours,** 6 ± ~~1~~**0.5** hours, 12 ± ~~1~~**0.5** hours, 24 ± ~~1~~**0.5** hours, **30 ± 2 hours,** 48 ± 2 hours, 72 ± 2 hours **and 96 ± 2 hours**)
    Purpose for Change: Need to align with (CPMP/BPWG/220/02) to include 15 min, 3 hr and 30 hr PK sampling timepoints.

21. Section 20.2.1 – Table 7
    Description of Change:
    The details for summary schedule of visit assessment for surgical bleeding added in new subsection.
    Purpose of Change: The details for surgery related visit added for further clarification, to address this possibility for subjects on year-long prophy study who could require surgical procedure during this time.

22. Section 20.3 - Table 8
    Description of Change:
    Removal of Immunogenicity 'X' in baseline visit/post-infusion column
    Purpose of Change: To correct error on clinical laboratory assessment chart.

23. Section 20.3 - Table 8
    Description of Change:
    Removal of blood group 'X' from 6-month follow-up visit
    Purpose of Change: To correct error on clinical laboratory assessment chart.

24. Section 20.3 - Table 8
    Description of Change:
    Original text:
    Footnote c) Coagulation panel/PK assessment:
    New text:
    Footnote c) Coagulation panel/PK assessment **(also refers to IR pre/post dose assessments at each follow-up visit)**:
    Purpose of Change: To clarify the information.

25. Section 20.3– Table 8

Description of Change:

Original text:

Footnote c) once the PK infusion is completed 30 ± 5 minutes, 60 ± 5 minutes, 6 ± 1 hours, 12 ± 1 hours, 24 ± 2 hours, 48 ± 2 hours, 72 ± 2 hours

Footnote m) Blood samples will be drawn within 30 minutes pre-infusion, and at 7 time points post-infusion (30 ± 5 minutes, 60 ± 5 minutes, 6 ± 1 hours, 12 ± 1 hours, 24 ± 2 hours, 48 ± 2 hours, 72 ± 2 hours)

New text:

Footnote c) once the PK infusion is completed **15 ± 5 minutes,** 30 ± 5 minutes, 60 ± 5 minutes, **3 ± 0.5 hours,** 6 ± ~~1~~**0.5** hours, 12 ± ~~1~~**0.5** hours, 24 ± ~~1~~**0.5** hours, **30 ± 2 hours,** 48 ± 2 hours, 72 ± 2 hours **and 96 ± 2 hours**)

Footnote m)

Blood samples will be drawn within 30 minutes pre-infusion, and at ~~7~~**11** time points post-infusion (**15 ± 5 minutes,** 30 ± 5 minutes, 60 ± 5 minutes, **3 ± 0.5 hours,** 6 ± ~~1~~**0.5** hours, 12 ± ~~1~~**0.5** hours, 24 ± ~~1~~**0.5** hours, **30 ± 2 hours,** 48 ± 2 hours, 72 ± 2 hours **and 96 ± 2 hours**)

Purpose for Change: Need to align with (CPMP/BPWG/220/02) to include 15 min, 3 hr and 30 hr PK sampling timepoints.

26. Section 20.3.1 – Table 9

Description of Change:

The details for laboratory sampling for surgical bleeding added in new subsection

Purpose of Change: The details for surgery related visit added for further clarification, to address this possibility for subjects on year-long prophy study who could require surgical procedure during this time

INVESTIGATOR ACKNOWLEDGEMENT

RECOMBINANT VON WILLEBRAND FACTOR (rVWF)

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

CLINICAL TRIAL PHASE 3

GLOBAL AMENDMENT 3: 2017 AUG 03

Replaces: AMENDMENT 2: 2016 DEC 15

OTHER PROTOCOL ID(s)
NCT Number: NCT02973087
EudraCT Number: 2016-001478-14
IND NUMBER: 013657

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT

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A prospective, phase 3, open-label, international multicenter study on efficacy and safety of prophylaxis with rVWF in severe von Willebrand Disease

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By signing below, the investigator acknowledges that he/she has read and understands this protocol, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
[redacted], MD
[redacted]
Global Clinical Development Operations
Baxalta Innovations GmbH

CLINICAL STUDY PROTOCOL

PRODUCT: Recombinant Von Willebrand Factor (rVWF, vonicog alfa)

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 SHORT TITLE: rVWF IN PROPHYLAXIS

PROTOCOL IDENTIFIER: 071301

CLINICAL TRIAL PHASE 3

GLOBAL AMENDMENT 6: 2018 MAR 12

Replaces:
AMENDMENT 3: 2017 AUG 03

ALL VERSIONS:
Amendment 6: 2018 MAR 12
Local (Czech) Amendment 5: 2017 AUG 08
Local (Germany) Amendment 4: 2017 AUG 04
Amendment 3: 2017 AUG 03
Amendment 2: 2016 DEC 15
Amendment 1: 2016 APR 08
Original: 2014 FEB 09

OTHER ID(s)
NCT Number: NCT02973087
EudraCT Number: 2016-001478-14
IND NUMBER: 013657

Study Sponsor(s):

Baxalta US Inc.
300 Shire Way
Lexington, MA 02421,US

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna, AUSTRIA

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted]
Global Clinical Development Operations
Baxalta Innovations GmbH

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (e.g. investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) and suspected unexpected serious adverse events (SUSARs) to the ECs.

ALL SAEs, INCLUDING SUSARs, ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT.

Bleeding events that meet seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) should be reported on the SAE eCRF and SAE Report form as an SAE.

Drug Safety contact information:

Baxalta Global Drug Safety fax number: [redacted]

OR

email: [redacted]

For definitions and information on the assessment of these events, refer to the following:

- Adverse Events (AEs), Section 12.1
- SAEs, Section 12.1.1.1
- SUSARs, Section 12.1.1.2
- Assessment of AEs, Section 12.1.2
- Safety Reporting, Section 12.1.2.3

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	Recombinant von Willebrand factor (rVWF, vonicog alpha)
Name(s) of Active Ingredient(s)	Recombinant von Willebrand factor (rVWF, vonicog alpha)
CLINICAL CONDITION(S)/INDICATION(S)	
Subjects with severe von Willebrand disease (VWD) (baseline VWF: Ristocetin cofactor activity (VWF:RCo) <20 IU/dL) requiring prophylactic treatment with coagulation factor replacement	
PROTOCOL ID	071301
PROTOCOL TITLE	A prospective, phase 3, open-label, international multicenter study on efficacy and safety of prophylaxis with rVWF in severe von Willebrand disease
Short Title	rVWF in prophylaxis
STUDY PHASE	Phase 3
PLANNED STUDY PERIOD	
Initiation	2017 OCT
Primary Completion	2019 Q4
Study Completion	2019 Q4
Duration	27 months
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
The purpose of this phase 3 study is to investigate the efficacy and safety, including immunogenicity, thrombogenicity and hypersensitivity reactions, as well as pharmacokinetics (PK), [redacted] and [redacted] of prophylactic treatment with rVWF (vonicog alfa) in adult subjects with severe VWD.	
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.	
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 FVIII activity	

Exploratory Objectives	
[redacted] rk	
STUDY DESIGN	
Study Type/ Classification/ Discipline	Efficacy and Safety
Control Type	No control
Study Indication Type	Prophylaxis and treatment of bleeding episodes
Intervention model	Single-group
Blinding/Masking	Open-label
Study Design	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, [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 (pdVWF switch subjects) will receive prophylactic treatment with rVWF (vonicog alfa) for a 12-month period.
Planned Duration of Subject Participation	Approximately 15 months
Primary Outcome Measure	
Efficacy • Annualized bleeding rate (ABR) for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa)	
Secondary Outcome Measures	
Additional efficacy of prophylactic treatment with rVWF (vonicog alfa) • ABR percent reduction success for OD subjects defined as at least 25% reduction of ABR for spontaneous (not related to trauma) bleeding episodes during rVWF (vonicog alfa) prophylaxis relative to the subject's own historical ABR during on-demand treatment	

- ABR preservation success for pdVWF switch subjects 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 during prophylactic treatment with pdVWF
- Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 bleeding episodes during the 12-month 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
- Spontaneous ABR 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)

Safety

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

Pharmacokinetics (PK) and Pharmacodynamics (PD)

- PK parameters after a washout for on-demand 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 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 VWF:RCo, Von Willebrand factor antigen (VWF:Ag), Von Willebrand collagen binding activity (VWF:CB).
- PD parameters after a washout for on-demand subjects: C_{max}, T_{max}, and $AUC_{0-tlast}$ as measured in FVIII activity by the 1-stage clotting assay (FVIII:C).
- PK parameters at steady state for on-demand and switch subjects: area under the concentration versus time curve from 0 to end of the partial dosing interval ($AUC_{0-tau;ss}$), 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. PK parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.
- PD parameters at steady state for on-demand and switch subjects: $AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$ as measured in FVIII actvitiy by the 1-stage clotting assay (FVIII:C). PD parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.
- Time course of FVIII clotting activity (FVIII:C) levels.

Exploratory Outcome Measures	
[redacted]	
INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**Dosage form**: powder and solvent for solution for injection **Dosage frequency**: Prophylactic Treatment Subjects transitioning from on-demand treatment will receive twice weekly infusion with rVWF (vonicog alfa) at doses of 50 ± 10 IU/kg rVWF:RCo. Dosage may be individualized within this range based on: • available historical PK data • type and severity of bleeding episodes the subject has experienced in the past • monitoring of appropriate clinical and laboratory measures

	The starting dose can, after consultation with the Sponsor, be increased up to 80 U/kg if considered necessary to assure effective prophylaxis. Subjects switching from pdVWF prophylaxis treatment: the weekly dose (IU/kg) of rVWF (vonicog alfa) for each patient will be equivalent (± 10%) to the weekly VWF dose received during prophylactic treatment with pdVWF. The weekly dose should be divided into 2 infusions, 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. A once weekly dose regimen will be allowed after switch to rVWF (vonicog alfa) if the patient has been on a once weekly dose regimen with pdVWF. Dose and dose interval may, after consultation with the sponsor, be further individualized based on: • available historical PK data • type and severity of bleeding episodes the subject has experienced in the past • monitoring of appropriate clinical and laboratory measures <u>Treatment of Bleeding Episodes:</u> Dosage must be individualized based on the subject's weight, type and severity of bleeding episode and monitoring of appropriate clinical and laboratory measures. In general, an initial dose of 40-60 IU/kg VWF:RCo with or without 30-45 IU rFVIII [ADVATE, octocog alfa]/kg is recommended (rVWF:rFVIII ratio of 1.3:1: ± 0.2). In cases of major bleeding episodes, a dose of up to 80 IU/kg VWF:RCo may be infused. Subsequent doses, if necessary, will be administered with or without ADVATE (rFVIII, octocog alfa) to maintain VWF:RCo and FVIII levels for as long as deemed necessary by the investigator. **Mode of Administration:** intravenous
SUBJECT SELECTION	
Targeted Accrual	Approximately 22 adult subjects with severe VWD will be included to have ≥8 subjects in each cohort (OD and switch). A total of at least 5 type 3 VWD subjects will be followed for 12 months.
Number of Groups/ Arms/ Cohorts	Single-group

Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding:
    a. Type 1 (VWF:RCo <20 IU/dL) or,
    b. Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2M or,
    c. Type 3 (VWF:Ag ≤3 IU/dL).
2. Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.
3. For on-demand patient group, subject currently receiving on-demand treatment for whom prophylactic treatment is recommended by the investigator.
4. For pdVWF switch patient group, subject has been receiving prophylactic treatment of pdVWF products for no less than 12 months prior to screening.
5. For on-demand patient group, subject has ≥3 documented spontaneous bleeds (not including menorrhagia) requiring VWF treatment during the past 12 months.
6. Availability of records to reliably evaluate type, frequency and treatment of bleeding episodes during at least 12 months preceding enrollment. Up to 24 months of retrospective data should be collected if available. Availability of dosing and factor consumption during 12 months (up to 24 months) of treatment prior to enrollment is required for pdVWF switch subjects and is desired (but not a requirement) for on-demand subjects.
7. Subject is ≥18 years old at the time of screening and has a body mass index ≥15 but <40 kg/m^2.
8. If female of childbearing potential, subject presents with a negative blood/urine pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.
9. Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

Subjects who meet ANY of the following criteria are not eligible for this study:

1. The subject has been diagnosed with Type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD (e.g., qualitative and quantitative platelet disorders or elevated prothrombin time (PT)/international normalized ratio [INR] >1.4).
2. The subject is currently receiving prophylactic treatment with more than 5 infusions per week.
3. The subject is currently receiving prophylactic treatment with a weekly dose exceeding 240 IU/kg.
4. The subject has a history or presence of a VWF inhibitor at screening.
5. The subject has a history or presence of a FVIII inhibitor with a titer ≥0.4 Bethesda units (BU) (by Nijmegen modified Bethesda assay) or ≥0.6 BU (by Bethesda assay).
6. The subject has a known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins.
7. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
8. The subject has a medical history of a thromboembolic event.

9. The subject is human immunodeficiency virus (HIV) positive with an absolute Helper T cell (CD4) count <200/mm^3.
10. The subject has been diagnosed with significant liver disease per investigator's medical assessment of the subject's current condition or medical history or as evidenced by any of the following: serum alanine aminotransferase (ALT) greater than 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).
11. The subject has been diagnosed with renal disease, with a serum creatinine (CR) level ≥2.5 mg/dL.
12. The subject has a platelet count <100,000/mL at screening.
13. The subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to signing the informed consent.
14. The subject is pregnant or lactating at the time of enrollment.
15. Patient has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
16. The subject has participated in another clinical study involving another investigational product (IP) or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
17. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
18. The subject is scheduled for a surgical intervention.
19. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
20. The subject has a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
21. The subject is in prison or compulsory detention by regulatory and/or juridical order
22. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.

Delay criteria

1. If the subject presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) the screening visit will be postponed until the subject has recovered.

STATISTICAL ANALYSIS

Sample Size Calculation

Approximately 22 adult subjects with severe VWD will be included in the study. The aim is to have ≥8 subjects in each cohort (OD and switch). A total of at least five type 3 VWD subjects will be followed for 12 months. 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).[1]

Planned Statistical Analysis

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

The Safety Analysis Set will be composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

The Per-Protocol (PP) Analysis Set will be composed of subjects who are at least 70% compliant regarding the number of scheduled prophylactic infusions. Only subjects who meet all study entry criteria and who have no major protocol violations that might impact primary efficacy assessments will be included in the PP analysis set.

The Pharmacokinetic Full Analysis Set (PKFAS) will be composed of all subjects who received the PK infusion and who provided acceptable data for PK and PD analysis. Acceptable PK/PD data will be defined in the Statistical Analysis Plan.

Primary Outcome Measure:

No formal statistical hypothesis test is planned for the analysis. Spontaneous ABR while treated with rVWF (vonicog alfa) for each cohort, on demand and switch subjects, will be estimated using a negative binomial regression. The prior ABR for each cohort will be based on historical data collected from each enrolled subject. The two ABRs (observed on the study and historical) will be assessed 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 ABR ratio together with a two-sided, 95% confidence interval (CI) will be reported for each cohort.

The difference in on-study ABR relative to historical ABR will be summarized descriptively.

The primary efficacy analysis will be based on the FAS and will be summarized by the two cohorts: on-demand and switch subjects. As a supportive analysis, the same analysis will also be carried out on the per-PP analysis set.

Secondary Outcome Measures:

In general, data for secondary efficacy analysis will be summarized by the two cohorts: on-demand and switch subjects and when applicable overall. Mean, standard deviation, median, range, quartiles will be calculated for continuous endpoints. Proportions will be calculated for categorical endpoints. Confidence intervals at the 95% level will be provided when appropriate.

Additional efficacy of prophylactic treatment with rVWF (vonicog alfa):

The number and proportion of on-demand subjects with ABR percent reduction success (i.e. $\geq 25\%$) will be calculated together with a two-sided 95% CI for the proportion.

The number and proportion of pdVWF switch subjects with ABR preservation success will be reported together with the corresponding 95% two-sided CIs for the proportion.

The number and proportion of subjects with categorized spontaneous ABR (i.e. 0, 1-2, 3-5, more than 5 bleeds) will be reported descriptively.

Summary statistics for the total number of infusions, as well as average number of infusions per week will be provided. The total weight adjusted consumption of rVWF (vonicog alfa) during prophylactic treatment will be provided. If applicable, historical data on consumption of pdVWF prior to the study will be summarized as well.

The change in spontaneous ABR from the historical rate to that during the rVWF (vonicog alfa) prophylaxis period will be summarized by location of bleeding (GI, epistaxis, joint bleeding, menorrhagia, oral and other mucosa, muscle and soft tissue, etc.).

Pharmacokinetics (PK) and Pharmacodynamics (PD):

The following PK parameters, based on the initial PK assessment after a washout for on-demand subjects, will be listed and summarized descriptively for VWF:RCo, VWF:Ag and VWF:CB: IR, $T_{1/2}$, MRT, $AUC_{0-\infty}$, $AUC_{0-tlast}$, C_{max}, T_{max}, V_{ss}, and CL. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity (FVIII:C), based on the initial PK assessment after a washout for on-demand subjects will be assessed using C_{max}, T_{max}, and $AUC_{0-tlast}$. These PD parameters will be listed and summarized descriptively.

PK parameters at steady state ($AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$) for the partial dosing interval will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study for VWF:RCo, VWF:Ag and VWF:CB and summarized descriptively for subjects with the same dosing regimens. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity (FVIII:C) will be assessed using $AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$. These PD parameters will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study and will be summarized descriptively for subjects with the same dosing regimens.

For the on-demand subjects, the PK of VWF:RCo will be analyzed using a population PK approach to characterize the single and multiple dose pharmacokinetics, including associated variability, of VWF:RCo in the study population.

For the switch subjects, differences in $AUC_{0-tau;ss}$, $C_{max;ss}$, and $C_{min;ss}$ assessess shortly after reaching steady state and assessed at the end of the study will be assessed by ratio of geometric means and corresponding two-sided 95% confidence intervals for VWF:RCo, VWF:Ag, VWF:CB, and FVIII:C. 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.

Descriptive statistics will be used to summarize VWF:RCo, VWF:Ag, VWF:CB, and FVIII:C levels for each nominal time point on the PK curve. For all subjects activity/concentration vs. time curves will be prepared.

Safety:

Safety analysis will be performed overall and by the two cohorts: on-demand and switch subjects.

Treatment-emergent AEs (TEAEs) are defined as AEs with start dates on or after the first exposure to IP. Summaries of AEs will be based on TEAEs unless otherwise indicated.

Occurrence of AEs and serious AEs (SAEs) will be summarized descriptively, by system organ class and preferred term. The number and percentage of subjects who experienced AEs and SAEs, and the number of AEs and SAEs will be tabulated. In addition, the number of subjects who experienced AEs assessed as related to IP by the investigator, and the number of IP-related AEs will be tabulated. The number of patients with AEs by severity will be presented similarly.

A listing of all AEs will be presented by subject identifier, age, sex, preferred term and 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.

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 infusion, irrespective of being related or not related to treatment. Temporally associated AEs will be presented in summary tables.

Adverse events of special interest (AESI), such as hypersensitivity reactions and thromboembolic events, will be monitored throughout the study and statistical analysis will be conducted based on the search criteria (eg, standardized MedDRA queries [SMQ]) determined prior to database lock, and summarized.

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.

Clinically significant changes relative to baseline in vital signs and clinical laboratory parameters (hematology, clinical chemistry) will be reported.

4. TABLE OF CONTENTS

Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABR	Annualized bleeding rate
ADAMTS13	A Disintegrin And Metalloproteinase with a Thrombospondin type 1 motif, number 13
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the plasma concentration /time curve from time 0 to infinity
$AUC_{0-tau;ss}$	Area under the plasma concentration /time curve from time 0 to end of the partial dosing interval
$AUC_{0-tlast}$	Area under the plasma concentration /time curve from 0 to the last measurable concentration
aPTT	Activated partial thromboplastin time
B19V	Parvovirus B19
BP	Blood pressure
BU	Bethesda Unit
BUN	Blood urea nitrogen
BW	Body weight
CAM	Cell adhesion molecule
CBC	Complete blood count
CD4	Helper T cell
CHO	Chinese hamster ovary
CI	Confidence interval
Cl	Chloride
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max;ss}$	Maximum plasma concentration during the partial dosing interval at steady state
$C_{min;ss}$	Minimum plasma concentration during the partial dosing interval at steady state
CR	Creatinine
CTA	Clinical Trial Agreement
eCRF	Electronic case report form
DMC	Data monitoring committee
DIC	Disseminated intravascular coagulation

Abbreviation	Definition
DVT	Deep vein thrombosis
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
[redacted]	[redacted]
FAS	Full analysis set
FVIII	Factor VIII
FVIII:C	Factor VIII clotting activity
GCP	Good Clinical Practice
GI	Gastrointestinal
Glu	Glucose
HAMA	Human anti- mouse antibodies
HAV	Hepatitis A virus
HB	Hepatitis B
HBs	Hepatitis B surface
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
[redacted]	[redacted]
HRP	Horseradish peroxidase
IB	Investigator's brochure
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
INR	International normalized ratio
IP	Investigational product
IR	Incremental recovery
i.v.	Intravenous

Abbreviation	Definition
K	Potassium
k.o.	Knock out
LDH	Lactate Dehydrogenase
Na	Sodium
NMC	Non-medical complaint
NOAEL	No observed adverse effect level
MRI	Magnetic resonance imaging
MRT	Mean residence time
pdVWF	Plasma derived VWF product
pdVWF/FVIII	Plasma derived VWF product containing fractions of FVIII
PBAC	Pictorial Blood Assessment Chart
PCR	Polymerase Chain Reaction
PEF	Peak expiratory flow
PK	Pharmacokinetic
PKFAS	Pharmacokinetic Full Analysis Set
PKPPAS	Pharmacokinetic Per Protocol Analysis Set
PP	Per protocol
PT	Prothrombin time
Q1, Q3	Quartile
rFVIII	Recombinant factor VIII
rVWF	Recombinant von Willebrand factor
RBC	Red blood cell count
SAE	Serious adverse event
SAER	Serious adverse event report
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
[redacted]	[redacted]
SIC	Subject identification code
SMQ	Standardised MedDRA queries
sP-selectin	Soluble P-selectin
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Terminal phase half life
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack

Abbreviation	Definition
T_{max}	Minimum time to reach the maximum concentration
$T_{max;ss}$	Minimum time to reach the maximum concentration at steady state
TTP	Thrombotic thrombocytopenic purpura
ULMW	Ultra-large molecular weight
ULN	Upper limit of normal
V_{ss}	Volume of distribution at steady state
[redacted]	[redacted]
VTE	Venous thromboembolism
VWD	von Willebrand disease
VWF	Von Willebrand factor
VWF:Ag	Von Willebrand factor antigen
VWF:CB	Von Willebrand Factor collagen binding
VWF:RCo	Von Willebrand factor: Ristocetin cofactor activity
WBC	White blood cell

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

Baxalta US Inc. (hereafter referred to as Baxalta or sponsor) has developed a human recombinant von Willebrand Factor (rVWF, vonicog alpha), which is co-expressed with recombinant factor VIII (rFVIII) in a Chinese hamster ovary (CHO) cell line and separated during the subsequent downstream process. To address concerns regarding the risk of transmission of blood-borne pathogens that may be introduced by human plasma, no exogenously added raw materials of human or animal origin are employed in the cell culture, purification, or formulation of the final container product. The only proteins present in the final container product other than rVWF (vonicog alfa) are trace quantities of murine immunoglobulin (IgG, from the immunoaffinity purification), host cell (i.e., CHO) protein, rFurin (used to further process rVWF). rVWF (vonicog alfa) is intended for the treatment of von Willebrand disease (VWD).

rVWF (vonicog alfa) has been developed under the Baxalta internal code BAX111 and is used as investigational product (IP) in this study. rVWF (vonicog alfa) may be used with or without ADVATE (rFVIII, octocog alfa) for the treatment of bleeding episodes (see Section 8.6.4.4). See Section 8.6 for further information on the IPs and their usage in this study. A detailed description of rVWF (vonicog alfa) is also provided in the Investigator's Brochure (IB).

rVWF (vonicog alfa) was granted licensure in the United States in December 2015 under the brand name VONVENDI for the on-demand treatment and control of bleeding episodes in adults diagnosed with VWD; as of the date of this protocol VONVENDI is not yet available on the market.

6.2 Clinical Condition/Indication

Von Willebrand Factor (VWF) is a large multimeric glycoprotein with a molecular weight that varies from 500 to 20,000 kDa. VWF is normally found in plasma and produced in the alpha-granules of platelets and in endothelial cell organelles known as the Weibel-Palade bodies. VWF mediates platelet adhesion and aggregation at sites of vascular injury, one of the key functions in primary hemostasis. VWF also serves to stabilize coagulation factor VIII (FVIII), where FVIII is an essential cofactor of secondary hemostasis, which leads to fibrin clot formation.[2] Qualitative and/or quantitative deficiencies of VWF lead to a highly variable bleeding diathesis known as VWD, the most common of the hereditary coagulation factor deficiencies. Penetrance of VWD is highly variable, with only a small fraction of mildly affected patients displaying clinical symptoms or a family history of a bleeding diathesis.

The current biochemical-based classification distinguishes disorders arising from partial quantitative (type 1), qualitative (type 2), or virtually complete (type 3) deficiencies of VWF. Up to 70% of VWD patients are diagnosed with type 1 VWD, which may also be associated with minor functional defects in the molecule. In general, patients with type 1 VWD display mild clinical symptoms. Approximately 20 to 30% of VWD patients are diagnosed with type 2 VWD. Type 2 VWD is further divided into 4 subtypes (A, B, N, and M), reflecting distinct classes of functional abnormalities. These defects result in abnormal functional and/or multimeric distribution patterns that facilitate their diagnosis. The bleeding diathesis is usually moderate and primarily affects the mucosal tissues. Type 2N VWD patients are sometimes misdiagnosed as mild hemophilia A. Finally, approximately 1% percent of VWD patients exhibit a total or near total absence of VWF, which is classified as type 3 VWD. The incidence of type 3 VWD is estimated at 0.5-1.0 x 10^6. This type is also associated with a very low FVIII level (typically <5%) because the VWF carrier function for FVIII is lost. Replacement of VWF alone stabilizes endogenous FVIII, resulting in hemostatic levels within several hours post-infusion. Published results from studies of a plasma-derived VWF (pdVWF) concentrate demonstrated an increase of FVIII at an approximate rate of 5.8 ± 1 IU dL^{-1} h^{-1}.[3] Type 3 VWD patients display severe hemorrhagic symptoms with bleeding predominantly in mucosal tissues, muscle and joints. All VWD patients, particularly those with type 2 or type 3 VWD, are at an increased risk for life-threatening bleeding episodes.

6.3 The Role of Prophylaxis in the Management of VWD

The goals of long term prophylaxis in VWD are to maintain VWF and FVIII at sufficient levels to reduce the frequency and duration of bleeding episodes, the need for red blood cell transfusions, and the risk of complications, such as arthropathy.[4] In contrast to hemophilia, routine prophylaxis is not as established in VWD, although prophylaxis for patients with severe VWD was in use in Sweden already during the 1950s.[5] In those early days of VWD treatment, plasma FVIII concentrates containing VWF fractions were applied for replacement therapy, which then were followed by plasma derived VWF products containing fractions of FVIII (pdVWF/FVIII).

A Swedish cohort including 37 patients with type 3 VWD under prophylactic median treatment of 11 years (range 2 to 45 years) was retrospectively analyzed.[6,7] The doses used for prophylaxis, given once weekly for at least 45 weeks per year, were calculated based on 12 to 50 IU/kg body weight (BW) of FVIII clotting activity (FVIII:C) which approximately corresponded to 24-100 IU/kg von Willebrand factor: Ristocetin cofactor activity (VWF:RCo) considering that mainly Haemate with a known VWF:RCo/FVIII:C ratio of about 2 was used. An escalation of doses from 1 to 3 dose levels was allowed depending on the frequency and severity of bleeding episodes.

The results demonstrate that under long-term prophylaxis the number of bleeds could be reduced dramatically. Whereas the median value for bleeds per year was about 10 before prophylaxis this value could be reduced to less than 1 bleed per year during prophylaxis.

The benefit of prophylaxis for such indications was retrospectively also demonstrated in a cohort of Italian patients including type 3, 2A, 2M and type 1 patients. Prophylaxis was started after severe gastrointestinal or joint bleeding episodes and completely prevented bleeding episodes in 8 of these 11 patients and largely reduced the need of blood transfusions in the remaining 3. A regimen of 40 IU rVWF:RCo/kg was applied every other day or twice a week. A prospective study on prophylaxis, the PRO.WILL study, has been initiated in Italy.[8]

The results of a prospective study investigating the prophylaxis in children and young adults showed a significantly reduced bleeding frequency and bleeding score (3 vs. 0.07; 3 vs. 0. p<0.001) compared to the pre-prophylaxis values. The median dose was 40 (20-47) IU/kg VWF:RCo administered mainly twice weekly in 23 patients, 3 times a week in 7 patients and 4 times a week in 2 children.[9]

The VWD Prophylaxis Network initiated the VWD International Prophylaxis (VIP) trial to investigate the role of prophylaxis in patients with severe VWD including Type 1, 2, and 3. The dose of the factor replacement product was 50 IU /kgVWF:RCo. The frequency of the dose depended on the type of bleeding and could be increased from once weekly to twice weekly or 3 times per week. For the treatment of menorrhagia the dose of 50 IU/kg VWF:RCo was given on the first day of menses for 2 cycles. The frequency could be increased to Day 1 and 2 for 2 cycles or to Day 1, 2, and 3 of menses.

The study contains both retrospective and prospective study components. Results from the retrospective study component were published, including 61 subjects on prophylactic regimen in the past 6 months prior to enrollment or subjects with a history of prophylaxis over at least 6 month.[10] Differences in annualized bleeding rates (ABR) within individuals (during prophylaxis – before prophylaxis) were significant for those with primary indications of epistaxis (P = 0.0005), joint bleeding (P = 0.002) and GI bleeding (P = 0.001). The difference in the group whose primary indication for treatment was abnormally heavy bleeding at menstruation (n = 4) was not significant (P = 0.25). The reduction of mucosal bleeding likely not only dependents on normal circulating levels of active VWF, but also on the presence of discrete concentrations of normal VWF inside the platelets and within endothelial matrices. The low subject number (n=4) and the treatment scheme for menorrhagia on Days 1, 2, and 3 of menses which might represent rather on-demand than prophylactic treatment may also account for the outcome in this study.

Results from the prospective study component were reported recently.[11] Eleven subjects completed the study. Six subjects had type 2A, and 5 subjects had type 3 VWD. Six subjects presented with epistaxis, 3 with GI bleeding, and 2 with joint bleeding. Seven subjects had dose escalation above the first level. Among the 10 subjects with evaluable bleeding log data, the use of prophylaxis decreased the median ABR from 25 to 6.1 (95% confidence interval [CI] of the rate difference: -51.6 to -1.7), and the median ABR was even lower (4.0; 95% CI: -57.5 to -5.3) when the subjects reached their final dosing level. The authors concluded that this was the first prospective study to demonstrate that prophylaxis with VWF concentrates is highly effective in reducing mucosal and joint bleeding rates in clinically severe VWD.

The results of the VIP study and previous investigations suggest that VWD patients with recurrent bleeding episodes and severe menorrhagia will benefit from a prophylactic VWF replacement therapy. There is evidence that up to 40% of patients with type 3 VWD experience joint bleeding which can lead to hemophilic arthropathy. Other potential indications for prophylaxis include patients with type 2A or 2B VWD with recurrent gastrointestinal bleeding, menorrhagia or frequent epistaxis.[4] Long-term prophylaxis for most patients with type 3 VWD and in some patients with type 1 or 2 VWD, depending on the pattern of bleeding, may be the treatment option of choice. Although the main experience with long-term prophylaxis is with secondary prophylaxis, primary prophylaxis starting at young age is recommended to prevent arthropathy in patients with severe VWD.[12]

However, further studies are needed to develop evidence-based guidelines for prophylactic treatment in VWD.

6.4 Populations to be Studied

A total of approximately 22 eligible, adult subjects with severe VWD (baseline VWF:RCo <20 IU/dL) are planned to be enrolled. Two cohorts of patients will be included: patients currently receiving on-demand VWF treatment (OD subjects) and patients currently on prophylactic treatment with pdVWF (pdVWF switch subjects), and the aim is to have ≥8 subjects in each of the 2 cohorts, with a total of at least 5 type 3 VWD subjects followed for 12 months. Enrolled subjects (i.e., subjects who have signed the informed consent form) will be eligible to participate in the study if they meet all of the inclusion criteria (see Section 9.1) and none of the exclusion criteria (see Section 9.2).

6.5 Findings from Nonclinical and Clinical Studies

The following summarizes the key findings from relevant nonclinical studies as well as from the completed clinical studies **070701** (Phase 1 pharmacokinetics [PK] and safety in VWD), **071001** (Phase 3 safety and efficacy in the treatment of bleeding episodes in VWD), **071101** (Phase 3 efficacy and safety in VWD subjects undergo elective surgical procedures), **071104** (Phase 1 safety and PK in hemophilia A), and **071401** (Phase 3, expanded access in a single subject with VWD). Potential risks and efficacy of rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) are summarized in the following sections. For additional information on nonclinical and clinical Phase 1 results refer to the rVWF (vonicog alfa) IB.

6.5.1 Findings from Nonclinical Studies

6.5.1.1 Primary Pharmacodynamics

Efficacy of rVWF (vonicog alfa) combined with ADVATE (rFVIII, octocog alfa) was shown in VWD animal models, which have also low endogenous FVIII levels. Time to occlusion and stable thrombus formation was assessed in the carotid occlusion model in VWD mice. The results demonstrated that rVWF (vonicog alfa) in combination with ADVATE (rFVIII, octocog alfa) acted efficiently in a dose-dependent manner and had higher efficacy than rVWF (vonicog alfa) alone or plasma derived (pd)VWF. These results were confirmed in an additional study assessing blood loss and survival in a tail tip bleeding model in VWD mice. In a VWD dog, rVWF (vonicog alfa) stabilized canine FVIII in the circulation and significantly reduced the bleeding time.

6.5.1.2 Safety Pharmacology

The anaphylactoid and thrombogenic potential of the co-infusion of ADVATE (rFVIII, octocog alfa) and rVWF (vonicog alfa) and the co-infused product's effects on blood pressure, cardiac and respiratory function and parameters of coagulation activation were investigated in 4 in vivo studies in different animal models. Safety pharmacology studies in rats, guinea pigs, rabbits, and dogs revealed no risks for anaphylactoid and thrombogenic potential of ADVATE (rFVIII, octocog alfa) in combination with rVWF (vonicog alfa). All observations in safety pharmacology studies are considered to lie within the biological variability of animal models or occurred due to known species-specific anaphylactoid effects of excipients.

6.5.1.3 Pharmacokinetics

Pharmacokinetic studies of both rVWF (vonicog alfa) alone and combined with human rFVIII (rVWF+ADVATE) were conducted in VWD mice, VWD dogs, VWD pigs, rats, and cynomolgus monkeys. Human rVWF (vonicog alfa) stabilized the endogenous FVIII in VWD mice, VWD pigs, and VWD dogs. Furthermore, the hypotheses that the area under the curve (AUC) with rVWF alone and rVWF+ADVATE is not inferior to the AUC with pdVWF (Haemate P) was tested and confirmed statistically in normal rats. The PK characteristics of ADVATE (rFVIII, octocog alfa) were not affected by co-administration of rVWF (vonicog alfa) in cynomolgus monkeys. The PK data in the FVIII knock out (k.o.) mice model are inconclusive and might not be relevant for the clinical situation. However, a stabilizing effect of VWF on FVIII could be shown in a double k.o. model in a dose dependent manner.

6.5.1.4 Toxicology

Single dose toxicity studies were conducted in C57BL/6J-mice, VWD mice, rats, rabbits, and cynomolgus monkeys. Rats, rabbits, and cynomolgus monkeys showed no signs of toxicity. Signs of microthrombosis, an exaggerated pharmacological effect, were observed in mice. Mice are not capable of sufficiently cleaving the rVWF (vonicog alfa) subunit as murine disintegrin and metalloproteinase with a thrombospondin type 1 motif, number 13 (ADAMTS13) does not decrease the ultra-large molecular weight multimers of rVWF (vonicog alfa).[13] The observed symptoms of microthrombosis are interpreted as a species-specific exaggerated pharmacological effect. Studies evaluating the safety of repeated administration of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) (daily over 14 days) were performed in a rodent (rat) and non-rodent (cynomolgus monkey) species. Reversible signs of exaggerated pharmacological effects (regenerative anemia, thrombocytopenia, and treatment-related histopathologic changes in the heart, liver, and spleen) were observed in rats that were administered 1400 U VWF:RCo/kg /day + 1080 IU ADVATE/kg/day intravenously once daily for 14 days. Also, these findings are interpreted as a species-specific exaggerated pharmacological effect due to the low susceptibility of human rVWF (vonicog alfa) to cleavage by rodent ADAMTS13.[13] No toxicologically relevant changes were evident for clinical observations, body weight, feed consumption, ophthalmology, urinalysis, coagulation, and serum chemistry parameters, platelet aggregation, and gross pathology. rVWF (vonicog alfa) combined with ADVATE (rFVIII, octocog alfa) was well tolerated in cynomolgus monkeys after daily intravenous (i.v.) (bolus) administration of 100 U VWF:RCo/kg rVWF (vonicog alfa) combined with 77 IU/kg ADVATE (rFVIII, octocog alfa) over a period of 14 days. No adverse effects could be detected in this species.

There were no signs of hemolysis, thrombosis, or thrombocytopenia after repeated intravenous application of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa). Therefore, 100 U VWF:RCo/kg/day rVWF (vonicog alfa) with or without 77 IU/kg ADVATE (rFVIII, octocog alfa) was considered the no observed adverse effect level (NOAEL) in this study, which was the highest dose tested. Anti-drug antibodies, however, were formed in both species and resulted in a significant reduction in drug exposure after 14 applications as compared to a single application. These antibodies substantially reduced the systemic exposure to the test substance as compared to a single dose administration. No adverse effects due to antibody formation were observed in both species.

rVWF (vonicog alfa) combined with ADVATE (rFVIII, octocog alfa) was well tolerated locally and no genotoxic potential was evident after 2 in vitro and 1 in vivo genotoxicity study. A study on the influence of co-administration of VWF and ADVATE (rFVIII, octocog alfa) on the immunogenicity of ADVATE (rFVIII, octocog alfa) in 3 different hemophilic mouse models (E17 hemophilic Balb/c mice, E17 hemophilic C57BL/6J mice, and E17 hemophilic human F8 transgenic mice) showed that rVWF (vonicog alfa) does not negatively impact the immunogenicity of ADVATE (rFVIII, octocog alfa) in any of the three different hemophilic mouse models.

6.5.2 Findings from Clinical Studies

The clinical safety, efficacy and PK were assessed in 4 completed trials: one phase 1 study (**070701)**) and two phase 3 studies (**071001** and **071101**) that enrolled patients with VWD; one phase 1 study (**071104**) that enrolled patients with hemophilia A. Details on study design, populations enrolled, and safety and efficacy outcomes of the phase 1 studies are presented in Section 6.5.2.1 and Section 6.5.2.2, the phase 3 study in Section 6.5.2.3, and the phase 3 surgery study in Section 6.5.2.4. Information on a single subject with VWD in Study **071401** is presented in Section 6.5.2.5.

6.5.2.1 Study 070701

Phase 1 clinical study **070701** was a multicenter, controlled, randomized, single-blind, prospective 3-step, dose escalation study to investigate safety, tolerability, and PK of rVWF (vonicog alfa) combined at a fixed ratio with ADVATE (VWF:RCo/FVIII:C of 1.3 ± 0.2:1) in adults with severe VWD.[14] Subjects were enrolled in sequential cohorts in a dose escalating manner: Cohort 1, 2, and 3 received a single intravenous infusion of rVWF:ADVATE at the following doses: 2 IU/kg VWF:RCo (Cohort 1), 7.5 IU/kg VWF:RCo (Cohort 2), and 20 IU/kg VWF:RCo (Cohort 3). Subjects in Cohort 4 received a single intravenous infusion of rVWF:ADVATE and pdVWF/ADVATE at 50 IU/kg VWF:RCo in random order.

The primary endpoint was the tolerability and safety after single dose injections of rVWF:ADVATE at 2, 7.5, 20, and 50 IU/kg VWF:RCo for up to 30 days after the last IP infusion. The data generated in this phase 1 study suggest that rVWF:ADVATE up to the highest investigated dose of 50 IU/kg VWF:RCo is well tolerated and safe in adults with severe VWD. No thrombogenic risk or thrombotic thrombocytopenic purpura (TTP)-like syndrome was observed, and no neutralizing antibodies to VWF or FVIII were identified. There were no deaths or other serious adverse reactions, and no infusions were interrupted or stopped due to an AE. Overall, the reported AE profile was similar between the recombinant and plasma-derived concentrates.

Secondary endpoints were the PK assessment of VWF:RCo, von Willebrand factor antigen (VWF:Ag) and multimeric composition of rVWF (vonicog alfa) as well as FVIII:C at standardized time points after single injections of rVWF:ADVATE and pdVWF:FVIII.

The median VWF:RCo terminal half-life ($T_{1/2}$) of rVWF (vonicog alfa) at the 50 IU/kg dose was 16 hours. $T_{1/2}$ with pdVWF:FVIII at the same dose level appeared shorter at 12.58 hours, however, the limits of the 90% CI were similar (11.73 to 17.7 hours vs. 11.87 to 18.03 hours). The median $T_{1/2}$ of VWF:RCo were shorter with the lower investigated doses: 7.13 hours and 13.23 hours with the 7.5 IU/kg and 20 IU/kg doses, although these data were derived from a much smaller number of subjects.

In consequence of the missing ADAMTS13 cleavage, ultra-large molecular weight (ULMW) multimers are contained in the rVWF (vonicog alfa) final product. The immediate cleavage of these ultra-large multimers by ADAMTS13 upon release into the circulation could be demonstrated applying sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE)/Immunoblot with polyclonal anti-VWF antibodies to detect the resulting rVWF (vonicog alfa) subunit cleavage fragments.

Overall the data generated in this phase 1 study suggest that rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) is well tolerated and safe in adults with severe VWD.

6.5.2.2 Study 071104

This study was a prospective, uncontrolled, non-randomized, multicenter proof of concept study to assess safety and PK of the addition of rVWF (vonicog alfa) to ADVATE (rFVIII, octocog alfa) treatment in 12 evaluable subjects with severe hemophilia A. All subjects underwent 3 PK analyses: the first after infusion with ADVATE (rFVIII, octocog alfa) alone, the second after infusion with ADVATE (rFVIII, octocog alfa) plus 10 IU/kg rVWF (vonicog alfa) and the third after infusion with ADVATE (rFVIII, octocog alfa) plus 50 IU/kg rVWF (vonicog alfa).

The PK analysis was performed at intervals of approximately 8 to 14 days. Before each infusion for PK assessment, there was a wash-out period of at least 5 days and the subjects were not actively bleeding.

Primary outcome measures indicate that co-administration of rVWF (vonicog alfa) slightly sustain ADVATE activity with the highest observed ADVATE (rFVIII, octocog alfa) half-life of 13.74 h (CI 11.44 to 16.52) after co-infusion of 50 IU/kg ADVATE plus 50 IU/kg rVWF:RCo.

The highest improvement in ADVATE (rFVIII, octocog alfa) circulating half-life was observed in subjects with VWF:Ag levels below 100% which indicates an association between baseline VWF:Ag levels and ADVATE (rFVIII, octocog alfa) half-life increase.

No treatment related AEs or SAEs were reported. No subject withdrew due to an AE and there were no deaths. No binding antibodies to VWF, CHO, and rFurin were detectable in the confirmatory assay and no signs of a hypersensitivity to rVWF (vonicog alfa) or ADVATE (rFVIII, octocog alfa) antigen were observed. Laboratory values over time did not indicate any potential safety risk for hemophilia A patients treated with rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) in combination.

In summary, the data indicate that rVWF (vonicog alfa) co-administered with ADVATE (rFVIII, octocog alfa) up to the highest dose of 50 IU/kg VWF:RCo is well tolerated and safe in hemophilia A patients.

6.5.2.3 Study 071001

This was a phase 3, multicenter, open-label, part-randomized clinical study to assess the PK, safety, and efficacy of rVWF:rFVIII and rVWF in the treatment of bleeding episodes in adult subjects with severe type 3 and severe non-type 3 VWD.[15] A total of 49 subjects were enrolled (signed informed consent) and screened, 18 subjects were randomized (randomization only applies to Arm 1[PK50 with treatment of BE] and Arm 2 [PK50 only] see below), 37 subjects were treated with IP (all study arms), and 30 subjects completed the study.

The study consisted of 2 parts (Part A and Part B). Part A consisted of PK assessments alone (Arm 2: PK50 only [without treatment of bleeding episodes]), or PK assessments (Arm 1: PK50 and Arm 3: PK80) plus on-demand treatment period(s) of 6 months for bleeding episodes, or on-demand treatment for bleeding episodes only (Arm 4). Except for subjects in arm 2 who completed study after second PK assessment, subjects receiving treatment for PK assessments and/or bleeding episodes in Part A were to be entered into Part B to continue on-demand treatment for bleeding episodes for 6 additional months for a total of 12 months in the study.

The primary outcome measure was the number of subjects with "treatment success" (extent of control of bleeding episodes), which was defined as a mean efficacy rating score of <2.5 for a subject's IP-treated bleeding episodes during the study. The rate of subjects with treatment success was 100% (Clopper-Pearson exact 90% CI: 84.7 to 100.0) for bleeds where the assessments were made prospectively and excluding GI bleeds. Sensitivity analyses confirmed the results of the primary analysis.

Crossover results at 50 IU/kg VWF:RCo showed that the PK profile for rVWF (vonicog alfa) VWF:RCo was independent of administration alone or with rFVIII (ADVATE, octocog alpha) ($T_{1/2}$: 19.4 hours for rVWF and 16.6 hours for rVWF:rFVIII; IR: 1.8 U/dL per IU/kg infused for both rVWF and rVWF:rFVIII; mean residence time (MRT): 26.7 hours for rVWF and 25.2 hours for rVWF:rFVIII). FVIII levels increased substantially with a median peak at 24 hours of 111.0 U/dL for rVWF:rFVIII and 86.0 U/dL after rVWF alone, indicating that rVWF (vonicog alfa) induces a sustained increase in endogenous FVIII activity. The rVWF (vonicog alfa) PK profile was comparable at 50 IU/kg and 80 IU/kg VWF:RCo, and repeated PK at 80 IU/kg VWF:RCo showed close agreement between pretreatment and end-of-study results.

Further analysis of the PK data from the **071001** study supports the initial use of 50 IU/kg twice weekly for prophylaxis dosing in the present study for those subjects who are moving from on-demand to prophylaxis. Using 50 IU/kg for PK measurements, subjects in the **071001** study exhibiting a $T_{1/2}$ for rVWF of 14, 16, or 19 hours had rVWF plasma concentrations at 72 hours after administration of 2.55, 4.01, and 6.49% above baseline, respectively, and plasma concentrations at 96 hours after administration of 0.78, 1.40, and 2.71% above baseline, respectively. In this context it should be noted that subjects in the present study who have significant spontaneous bleeding while on twice weekly prophylaxis will have their regimen increased to 3 times per week based on clear criteria for different bleeding locations (for details see Section 8.6.4.3.1). Subjects in the present study who are switching from prophylaxis with a pdVWF product will begin on rVWF (vonicog alfa) using their same weekly total dose in IU/kg VWF:RCo used during their pdVWF prophylaxis divided into twice weekly infusions (for details see section 8.6.4.3).

A total of 125 AEs occurred in 25/37 (67.7%) subjects (62/318 infusions [19.5%]) during or after infusion with IP. Of these, 116/125 were non-serious (all mild or moderate; none were severe), and 9 SAEs were reported in 7 subjects. Of 125 total AEs, 38 were temporally associated with IP; 8 AEs were considered causally related to IP: 6 non-serious related AEs (tachycardia, infusion site paraesthesia, electrocardiogram [ECG] t-wave inversion, dysgeusia, generalized pruritis, and hot flush) occurred in 4 subjects, and 2 related SAEs (chest discomfort and increased heart rate) occurred in 1 subject. No deaths occurred during this study.

None of the subjects developed anti-VWF or anti-FVIII neutralizing antibodies and no binding antibodies to VWF or rFurin, or antibodies against CHO protein or anti-Murine IgG were observed. No clinical or subclinical signs or symptoms of a thrombogenic event were observed in this study. Following an initial increase in ultralarge VWF multimers after administration of rVWF (vonicog alfa), a notable decrease in the proportion of large VWF multimers occurred between 12 and 24 hours post infusion, due to degradation by the endogenous ADAMTS13 followed by a continued decline until the end of the 96-hour follow-up period.

Overall, the data support the safe and effective use of rVWF (vonicog alfa) with or without rFVIII (ADVATE, octocog alpha) in the treatment of bleeds in patients with VWD.

6.5.2.4 Study 071101

This was a phase 3, prospective, open-label, multicenter clinical study to evaluate efficacy and safety of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) in elective surgical procedures in adult subjects with severe VWD. A total of 24 subjects were enrolled (signed informed consent) and screened, 15 subjects were treated with rVWF (vonicog alfa), and 15 subjects completed the study.

Eleven subjects underwent a PK assessment by infusion of 50 ± 5 IU/kg rVWF:RCo at an infusion rate of up to 4 mL/min. 12 to 24 hours before surgery, subjects received a dose of 40 to 60 IU/kg rVWF:RCo. Within 3 hours prior to surgery, the subject's FVIII:C levels were assessed with a target of 30 IU/dL for minor and oral surgeries and 60 IU/dL for major surgeries. Within 1 hour prior to surgery, subjects received a dose of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) (depending on the target FVIII:C levels at the 3 hour assessment). VWF and FVIII IR and $T_{1/2}$ for each subject, when known, were used to guide the initial dose and subsequent doses.

The primary outcome measure was the overall assessment of hemostatic efficacy assessed by the investigator (hemophilia physician) 24 hours after last perioperative IP infusion or at completion of day 14 visit, whichever occurred earlier, and was summarized by the percentage of subjects in each efficacy category ("excellent", "good", "moderate" and "none"). Point estimate and corresponding 90% two-sided exact CI was calculated for the rate of subjects with an overall assessment of hemostatic efficacy. All 15 subjects treated with rVWF (vonicog alfa) (with or without ADVATE) for major (10), minor (4), and oral (1) elective surgical procedures had overall hemostatic efficacy ratings of "excellent" or "good". Most (73.3%) subjects had "excellent" overall hemostatic efficacy ratings; of these, 7 underwent major surgery and 4 underwent minor surgery. The remaining 26.7% subjects had "good" overall hemostatic efficacy ratings: 3 underwent major surgery and 1 underwent oral surgery. All 8 subjects with VWD Type 3, the subtype classified as absolute VWF deficiency, had overall hemostatic efficacy ratings of "excellent" (87.5%) or "good" (12.5%).

Intraoperative hemostatic efficacy ratings were also rated as "excellent" or "good" for all 15 treated subjects. Most (86.7%) subjects had "excellent" intraoperative hemostatic efficacy ratings; of these, 8 underwent major surgery, 4 underwent minor surgery, and 1 underwent oral surgery. Two (13.3%) subjects who underwent major surgery had "good" intraoperative hemostatic efficacy ratings. Intraoperative hemostatic efficacy was rated as "excellent" or "good" for all subjects with VWD Type 3: "excellent" for 7 (87.5%) subjects and "good" for 1 (12.5%) subject.

Only 1 subject received an intraoperative dose of rVWF (18.1 IU/kg) and ADVATE (8.1 IU/kg). The median daily postoperative weight-adjusted dose of rVWF (vonicog alfa) (with or without ADVATE) was 23.5 IU/kg on postoperative Day 1 (n=3) and 25.5 IU/kg on postoperative Day 14 (n=2). In subjects treated with rVWF:ADVATE, the daily postoperative weight-adjusted dose was 16.9 IU/kg rVWF and 7.6 IU/kg ADVATE on postoperative Day 1 (n=1) and decreased to 50.8 IU/kg rVWF and 7.6 IU/kg ADVATE on postoperative Day 7 (n=1). For subjects treated with rVWF alone, the median weight-adjusted dose (Q1, Q3) of rVWF was 35.4 IU/kg on postoperative Day 1 (n=2) and decreased to 23.7 IU/kg on postoperative Day 7 (n=4) and 25.5 IU/kg on postoperative Day 14 (n=2).

A total of 11 subjects were evaluated for PK in the study. As expected, postinfusion increases in concentrations of VWF:RCo, VWF:Ac, VWF:Ag, and VWF collagen binding (VWF:CB) were observed. Mean values for VWF:RCo were as follows: AUC0-∞/dose was 37.50 hours*IU/dL per IU/kg infused; AUC0-72h/dose was 34.08 hours*IU/dL per IU/kg infused; T1/2 was 17.83 hours; MRT was 24.32 hours; CL was 0.03117 dL/hour/kg; and volume of distribution at steady state (Vss) was 0.6837 dL/kg. Median values for VWF:RCo were as follows: AUC0-∞/dose was 32.94 hours*IU/dL per IU/kg infused; AUC0-72h/dose was 31.70 hours*IU/dL per IU/kg infused; T1/2 was 14.62 hours; MRT was 21.80 hours; CL was 0.03036 dL/hour/kg; and Vss was 0.7078 dL/kg. The VWF:RCo activity was consistent with that previously observed in clinical studies 071001 and 070701.

rVWF (vonicog alfa) was safe and well tolerated in adults with severe VWD undergoing major, minor, and oral elective surgical procedures. Of the 12 total treatment-emergent AEs (TEAEs) that occurred during the study, 2 deep vein thrombosis events (1 non-serious and 1 serious, as a part of one case) reported in one subject, who underwent total hip replacement surgery and who had concurrent condition of obesity, was assessed by the sponsor as possibly causally-related to study treatment. None of the TEAEs were either a severe allergic or hypersensitivity reaction or developed due to a severe allergic reaction.

One subject with VWD Type 3 who had an intraoperative transfusion of packed red blood cells during total knee replacement surgery tested positive for binding antibodies to VWF on postoperative Day 7 through study completion. No subjects developed neutralizing antibodies to rFVIII or binding antibodies to CHO, rFurin, or murine IgG.

In summary, the data support the safe and effective use of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) in achieving intra- and post-operative hemostasis in adult subjects with severe VWD undergoing major, minor, and oral elective surgical procedures.

6.5.2.5 Study 071401: Single Subject with von Willebrand Disease

One subject who exhibited allergic reactions to currently marketed pdVWF products was treated in the single-subject study **071401** with rVWF (vonicog alfa) only for the bleed treatment of continued hematuria, and for biopsy and surgical resection of a left-kidney mass.

For the initial rVWF (vonicog alfa) infusion, the subject received a test dose of 5% of the total dose of 60 IU/kg rVWF:RCo at an infusion rate of 1 mL/min. After a 10 to 15-minute observation period, no adverse symptoms or signs were noted and the subject received the remaining 95% of the total dose. The subject was monitored for any signs of an allergic reaction, and none were noted. Treatment with rVWF (vonicog alfa) every 12 to 24 hours was to continue at the discretion of the investigator based on VWF levels and clinical symptomatology. The subject had an excellent response and recovery, which allowed for daily dosing of rVWF (vonicog alfa) and, within 24 hours, the subject's bleeding had stopped. Daily dosing of rVWF (vonicog alfa) was maintained and the subject received his last dose on [redacted].

The subject also received rVWF (vonicog alfa) for 7 days for prophylaxis for surgery (surgical resection of a left-kidney mass). The subject experienced no hemorrhagic complications and no AEs that were considered related to the use of rVWF (vonicog alfa).

6.6 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

Current treatment of VWD patients relies on desmopressin and VWF products manufactured from pooled human plasma. Human VWF produced by recombinant technology could offer a new perspective in treatment of VWD. The benefit for the individual subject is anticipated to be significant during this clinical study. He/she may benefit from a product that minimizes excessive FVIII administration and thus allowing individualized dosing of VWF at optimal levels. Variations in VWF multimeric composition may lead to variability with respect to treating or preventing bleeds in VWD subjects, especially mucosal bleeds which are especially problematic. rVWF (vonicog alfa) product manufactured by Baxalta consistently contains ULMW VWF multimers due to the fact that the product has not been exposed to ADAMTS13.

The initial presence of these ULMW VWF multimers, which are subsequently cleaved by the subject's endogenous ADAMTS13, may result in improved platelet and collagen binding and therefore provide more predictable treatment outcomes.

By using a recombinant product, the risk of transmission of adventitious agents and other blood-borne pathogens associated with the use of products of human or animal origin has been eliminated. At this stage of product development, the key societal benefit is a better understanding of advanced treatment options for VWD and enhanced product availability.

These benefits outweigh the following identified or potential risks of rVWF (vonicog alfa):

- allergic-type hypersensitivity reactions as with any intravenous protein product
- the occurrence of thromboembolic events
- the development of neutralizing antibodies to VWF

Refer to the IB for further details on benefits and risks of the IP.

6.7 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996, with Addendum E6(R2) dated Nov 2016 EMA/CHMP/ICH/135/1995), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives 2001/20/EC and 2005/28/EC, the Declaration of Helsinki and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

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

7.2 Primary Objective

The primary objective of this study is to prospectively evaluate the 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.

7.3 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 FVIII activity

7.4 Exploratory Objectives

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

8. STUDY DESIGN

8.1 Overall Study Design

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

Subjects transitioning from on-demand treatment (OD subjects) or subjects switching from prophylactic treatment with pdVWF (pdVWF switch subjects) will receive prophylactic treatment with rVWF (vonicog alfa) for a 12-month period. The dose will be 50 ± 10 IU/kg rVWF twice weekly for OD subjects or will be based on their prior pdVWF dose for pdVWF switch subjects, and 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 Section 8.6.4.3).

The overall duration of prophylactic treatment with rVWF per subject will be 12 months.

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 Section 8.6.4.4.2).

The overall study design is illustrated in Figure 1.

8.2 Duration of Study Period(s) and Subject Participation

The overall duration of the study is approximately 27 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The subject participation period is approximately 15 months from enrollment to completion (i.e, last study visit), unless the subject is prematurely discontinued.

8.3 Outcome Measures

8.3.1 Primary Outcome Measure

8.3.1.1 Efficacy

- Annualized bleeding rate (ABR) for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa)

8.3.2 Secondary Outcome Measures

8.3.2.1 Additional efficacy of Prophylactic Treatment with rVWF (vonicog alfa)

- ABR percent reduction success for OD subjects defined as at least 25% reduction of ABR for spontaneous (not related to trauma) bleeding episodes during rVWF (vonicog alfa) prophylaxis relative to the subject's own historical ABR during on-demand treatment
- ABR preservation success for pdVWF switch subjects 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 during prophylactic treatment with pdVWF
- Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 bleeding episodes during the 12-month 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
- Spontaneous ABR 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)

8.3.2.2 Safety

- AEs: incidence, severity, causality
- Thromboembolic events
- Hypersensitivity reactions
- Development of neutralizing antibodies to VWF and FVIII
- Development of total binding antibodies to VWF and FVIII
- Development of binding antibodies to CHO proteins, mouse immunoglobulin G (IgG) and rFurin
- Clinically significant changes in vital signs and clinical laboratory parameters relative to baseline

8.3.2.3 Pharmacokinetics (PK) and Pharmacodynamics (PD)

- PK parameters after a washout for on-demand subjects: incremental recovery (IR), $T_{1/2}$, 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 VWF:Rco activity, VWF:Ag, VWF:CB activity.
- PD parameters after a washout for on-demand subjects: C_{max}, T_{max}, and $AUC_{0-tlast}$ as measured in FVIII activity by the 1-stage clotting assay (FVIII:C).
- PK parameters at steady state for on-demand and switch subjects: area under the concentration versus time curve from 0 to end of the partial dosing interval ($AUC_{0-tau;ss}$), 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. PK parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.
- PD parameters at steady state for on-demand and switch subjects: $AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$ as measured in FVIII activity by the 1-stage clotting assay. PD parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.
- Time course of FVIII clotting activity (FVIII:C) levels.

8.3.3 Exploratory Outcomes Measures

8.3.3.1 [redacted]

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

[redacted]

8.3.3.2 [redacted]

[redacted]

8.3.3.3 [redacted]

[redacted]

8.3.3.4 [redacted]

[redacted]

8.4 Randomization and Blinding

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

8.5 Study Stopping Criteria

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 (eg, 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.

The sponsor ultimately 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.

8.6 Investigational Product(s)

8.6.1 Packaging, Labeling, and Storage

8.6.1.1 rVWF (Recombinant von Willebrand Factor, vonicog alfa)

rVWF (vonicog alfa) will be packaged in boxes with 2 glass vials, one containing the rVWF powder, and the second vial containing the diluent (water for injection). Further details are provided in the IB and Pharmacy Manual. The rVWF label will include, at a minimum, the actual VWF:RCo potency and the date of expiration.

rVWF (vonicog alfa) is a powder that should be stored refrigerated (2-8°C [36-46°F]) . Deviations from the storage condition have to be communicated and followed up with the sponsor. Inadequately stored product will have to be placed in quarantine and may only be used after written IP administration authorization by the sponsor. After removal of the product from the refrigerator the product must not be returned to the refrigerator. The reconstituted product has to be used immediately (at least within 3 hours). rVWF (vonicog alfa) must not be used beyond the expiration date printed on the vial label. Avoid freezing at all times.

8.6.1.2 rFVIII (Recombinant Factor VIII, octocog alfa /ADVATE)

ADVATE (rFVIII, octocog alfa) will be packaged in boxes with 2 glass vials, one containing the lyophilized rFVIII, and the second vial containing the diluent. Further details are provided in the IB and Pharmacy Manual. The ADVATE label will include, at a minimum, the actual FVIII:C potency and the date of expiration.

ADVATE (rFVIII, octocog alfa) should be refrigerated (2-8°C [36-46°F]) in powder form and should not be used beyond the expiration date printed on the vial.

Deviations from the storage condition have to be communicated and followed up with the sponsor. Inadequately stored product will have to be placed in quarantine and may only be used after written IP administration authorization by the sponsor. After removal of the product from the refrigerator the product must not be returned to the refrigerator and has to be used immediately. Avoid freezing at all times.

8.6.2 Reconstitution

The reconstitution procedures for both rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) products are detailed in the Pharmacy Manual.

8.6.3 Administration

Following reconstitution, rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) (in case of bleeding episode treatment) should be administered to study subjects at room temperature and within 3 hours of reconstitution. The reconstituted rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa), should be inspected for particulate matter and discoloration prior to administration, whenever the solution and container permit. The solution should be clear and colorless in appearance. If not, do not administer the product. Plastic syringes provided by the sponsor must be used since coagulation factors tend to stick to the surface of glass syringes.

Investigational product infusions should be given at a slow enough rate to ensure the subject's comfort. The rate should not exceed 4 mL/minute The investigator/ subject shall ensure that no visible residual volume remains in the syringe(s) and that the complete content is administered. Upon completion of the infusion, the butterfly catheter should be flushed with at least 2 mL of saline solution. In case of a (central) venous access device, the flush should be with at least 10 mL of saline solution. The IP infusions should be administered over a duration of 2 to 20 minutes, depending on the volume.

Only the actual potencies of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) as stated on the vial labels and described in the Pharmacy Manual should be used. A variation of up to 10% of the intended dose for prophylactic infusions and of the intended dose for treatment of bleeding episodes is permissible and the exact dose should be recorded on the Case Report Form (CRF). Using of partial vials is not allowed.

At study visits where recovery analysis is being done, vials with the same lot numbers should be used throughout the PK IP infusion per subject.

For treatment of bleeding episodes, sequential administration will be done: separate syringes of the appropriate dose of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) will be prepared for sequential infusion. rVWF (vonicog alfa) should be infused first sequentially followed preferably within 10 minutes by infusion of ADVATE (rFVIII, octocog alfa). Only the actual potencies of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) as stated on the vial labels and described in the Pharmacy Manual should be used.

The final dose of rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) should be at a ratio of 1.3:1 ± 0.2.

8.6.4 Description of Treatment

8.6.4.1 PK-Assessment Treatment

For on-demand subjects, two PK assessments will be performed: an initial PK assessment after a wash-out period and a steady state PK assessments at the end of the study. The IP infusion for the initial PK assessment is scheduled on the baseline visit, which should be within 42 days after the completion of screening procedures and confirmation of eligibility. At the baseline visit the subjects will receive a dose of 50 ± 5 IU/kg rVWF:RCo for PK assessment. 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). A washout period of at least 5 days is required prior to infusion of rVWF (vonicog alpha) for PK assessment. The 2nd PK assessment for on-demand subjects will be performed at steady state at the end of the study(see Section 11.6). Subjects previously enrolled in rVWF studies **070701**, **071001** or **071101** and having previously undergone PK assessments in these studies are required to repeat the PK assessment due to different dose and time points used in these former studies.

For pdVWF switch subjects, two steady state PK assessments will be performed. The 1st PK will be assessed shortly after reaching steady state, which is expected to be 11 days after the 1st prophylactic dose for majority of the subjects, around the prophylactic dose #5-6. The 2nd PK will be at the end of the study. For steady state PK, 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) as long as it won't interfere with subject's the normal dosing schedule, otherwise the 96 hr sampling can be omitted (see Section 11.6). Final sample for PK analysis should be taken before next dose is administered.

8.6.4.2 Prophylaxis Initiation Treatment

The rVWF (vonicog alfa) prophylaxis initiation treatment visit will coincide with the 96 ± 2 h initial PK assessment for on-demand subjects. For pdVWF switch subjects, the rVWF (vonicog alfa) prophylaxis initiation treatment visit should occur within 42 days after the completion of screening procedures and confirmation of eligibility. At this visit subjects will receive their prophylaxis initiation dose. The prophylaxis doses are described in Section 8.6.4.3.

The subject will be trained on IP reconstitution and administration and may then qualify for home treatment (see Section 8.6.4.3.2). Refer toTable 6 (a/b) for study procedures and Table 8(a/b) for clinical laboratory assessments.

8.6.4.3 Prophylaxis Treatment

For on-demand subjects, the standard prophylactic dose is 50 ± 10 IU/kg rVWF:RCo, which may be increased up to 80 IU/kg. All on-demand subjects will initially receive rVWF (vonicog alfa) twice per week (Table 1, Schedule A). Examples of all dosing schedules are provided in Table 1.

For pdVWF switch subjects, the weekly dose (IU/kg) of IP for each patient 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 (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 (Table 1, Schedule B). A once weekly dose regimen will be allowed after switch to rVWF (vonicog alfa) only if the patient has been on a once weekly dose regimen with pdVWF.

Table 1
rVWF (vonicog alfa) Dosing Schedule Examples: Schedules A and B

Example	M	T	W	Th	F	Sat	Sun	M	T	W	Th	F	Sat	Sun
Schedule A	X				X			X				X		
Schedule B	X		X			X		X		X			X	

The prophylaxis dose may be further individualized within the range based on:

- available historical PK data
- type and severity of bleeding episodes the subject has experienced in the past and
- monitoring of appropriate clinical and laboratory measures

The individualized prophylaxic dose assignment will have to be agreed with the sponsor in advance, and the rationale should be well documented.

8.6.4.3.1 Adjustment of Dose or Dose Interval

In general, the dose and/or dose interval for each subject should not be changed unless prompted by clear medical needs. Dose and frequency adjustments should be agreed with the sponsor in advance unless it constitutes an urgent safety measure. The rationale for dosing adjustments needs to be documented in the subject's medical record.

For both OD and switch patients, dose escalations (not exceeding the upper dose limit of 80 IU/kg rVWF:RCo) and increase of dose frequency will only be allowed in case of insufficient therapeutic response with breakthrough bleeding episodes. The criteria for dose and/or frequency escalation are specific to each bleeding indication but, overall, involve 1 significant breakthrough bleeding episode despite the subject being compliant with scheduled prophylaxis treatment. For switch patients who require a dose escalation due to a breakthrough bleed, the frequency should be kept the same but the dose (IU VWF:RCo per infusion) should be increased up to 80 IU VWF:RCo. Following that, increases in frequency may be considered upon consultation with the Sponsor. For on demand subjects who require a dose escalation, at the discretion of the PI upon consultation with the Sponsor, the frequency may be kept the same but the dose (IU VWF:RCo per infusion) should be increased up to 80 IU VWF:RCo. If this proves to be insufficient, then the dosing frequency may be increased in these subjects. Table 2 presents the criteria for dosing escalation per each bleeding indication taken 50 ± 10 IU VWF:RCo/kg twice weekly dose as an example of subject's assigned starting dose. The criteria are applicable for both OD and switch subjects who were initially assigned to twice weekly dosing. Subjects entering the study will begin prophylaxis treatment according to Schedule A (Table 1) and will remain at this dose and frequency until meeting the criteria for escalation to the next higher schedule: for example, from 2 infusions of 50 ± 10 IU VWF:RCo/kg/week to 3 infusions of 50 ± 10 IU VWF:RCo/kg/week (Schedule B) to achieve an adequate therapeutic response. If a subject started with a weekly dose (possible for switch subjects), similar criteria would apply except that the subject will be excalated to twice weekly dosing if frequency change is necessary.

Table 2
Criteria for Escalation Specific to Each Bleeding Indication

	Schedule A	Schedule B
Joint bleeding	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a spontaneous joint bleeding episode occurs while on this regimen, the subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B following its resolution	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
GI bleeding	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a severe GI bleeding episode, i.e., requiring red blood cell transfusion, occurs while on this regimen, the subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B following its resolution	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Menorrhagia	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) on days 1 and 2 of menses for 2 cycles. Menstrual flow will be monitored by the PBAC score. If the average pictorial chart score is > 185, then the subject will escalate to up to 80 IU/kg or, if necessary, to Schedule B	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) on days 1, 2, and 3 of menses. Menstrual flow will be monitored by the PBAC score.
Epistaxis	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. The subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B in the event of 1 occurrence of breakthrough bleeding requiring intervention such as iron replacement therapy, transfusion, packing, hospitalization; or 2 bleeding events that require treatment with factor replacement	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Oral and Other Mucosa	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. The subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B in the event of 1 occurrence of breakthrough bleeding requiring intervention such as iron replacement therapy, transfusion, packing, hospitalization; or 2 bleeding events that require treatment with factor replacement.	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Muscle and Soft Tissue	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a spontaneous bleeding episode occurs while on this schedule, the subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B following its resolution.	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.

Abbreviations: GI: gastrointestinal; PBAC: Pictorial Blood Assessment Chart.

If a subject does not adequately respond to rVWF (vonicog alfa) therapy, he/she will be evaluated for the presence of neutralizing and total binding anti-VWF antibodies (see Section 12.9.3.2).

If a subject experiences a bleed while receiving rVWF (vonicog alfa) three times per week, the investigator should treat the bleed with rVWF (vonicog alfa) at doses up to 80 IU VWF:RCo/kg at a frequency determined by the investigator until the bleed resolves. Upon resolution of the bleeding event, the subject will return to their assigned prophylaxis regimen.

It is essential for the success of this study that the subjects adhere to treatment regimens. Therefore, procedures for monitoring subject's compliance are implemented (see Section 10.7).

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. For example, a subject routinely infuses IP on Monday and Thursday, he/she misses the Monday time point and therefore may infuse the IP on the next day (Tuesday) and thereafter proceed with infusing the IP on Thursday (considering a minimum 12 hours between the infusions) and return to the initial schedule.

If more than 30% of infusions of IP are missed within the visit interval of 3 months the subject will be discontinued from the study (see Section 9.4).

8.6.4.3.2 General Instructions for Home Treatment for Prophylaxis

At the discretion of the investigator, a subject may be considered suitable for home treatment only after the subject has received at least 1 infusion of IP in the clinic, either during planned prophylactic IP exposure or during the treatment of bleeding episodes, and meets the following additional criteria:

1. Fully understands the concept of a clinical study and related documentation (documented training of at least 30 minutes),
2. Has a history of previous experience with home treatment including self-administration and treatment with VWF containing concentrates,
3. Has adequate time for initial training of the study drug preparation (preparation, mixing and infusion of the IP(s) (documented training of at least 30 minutes).

This applies both to subjects who were on prior on-demand treatment and to subjects switching form prophylaxis with pdVWF. In the event a healthcare professional is required to administer IP, he/she must be trained and qualified by the investigator on the above procedures prior to the decision for home treatment. A Subject Guideline detailing all instructions and information listed above will be provided to each subject.

8.6.4.4 Treatment of Bleeding Episodes

8.6.4.4.1 General Instructions for Home Treatment of Bleeding Episodes

If a subject experiences a bleeding episode, he/she should contact the study site immediately and the site investigator should provide instructions on the treatment regimen. If the subject initiates the treatment at home, he/she should at least follow up with the study site if a visit is needed as per the standard of care at the center.

In the event a healthcare professional is required to administer treatment at the subject's home, he/she must be trained and qualified by the site investigator on the above procedures prior to the decision for home treatment. Once a subject has received 1 infusion of rVWF (vonicog alfa) in the clinic (either during planned IP exposure or during the treatment of a bleeding episode) and meets the criteria for home treatment, the treatment of bleeding episodes with IP can be conducted at home (see Section 8.6.4.3.2).

If a subject is not qualified for home treatment, rVWF (vonicog alfa) infusions must be administered at the study site.

If a subject experiences a bleeding episode that requires treatment between the screening and the prophylaxis initiation visit, the subject will be treated with IP (rVWF with or without ADVATE). Treatment with IP must occur at the study site unless the subject has previously qualified for home treatment with rVWF (vonicog alfa). If rVWF (vonicog alfa) treatment is not feasible, the subject may use his/her standard of care, such as commercial pdVWF/FVIII products. In any case a washout period of at least 5 days is required prior to rVWF (vonicog alfa) PK infusion at the initial PK assessment visit for on-demand subjects.

If a subject experiences a bleeding episode requiring treatment during the PK assessment, rVWF (vonicog alfa) should be used to treat the bleed. Blood draws for PK assessment will be stopped and the PK assessments will be repeated once the bleed has resolved and the subject is free of any symptoms related with the bleeding episode. Dose and frequency of rVWF (vonicog alfa) infusions or any other replacement therapy to stop the bleed should be recorded in the electronic Case Report Form (eCRF), and the reason for the use of any non-IP product or therapy should be documented.

8.6.4.4.2 Dosing Recommendations for Treatment of Bleeding Episodes

If an acute bleeding episode occurs, the subject will be treated with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa). It is the sponsor's opinion that, in many cases, treatment with ADVATE (rFVIII, octocog alfa) may not be necessary, since rVWF (vonicog alfa) prophylaxis will serve to increase endogenous FVIII levels. However, if endogenous FVIII is below 30-40 % or is unknown and cannot be estimated from the subject's PK study, an infusion of rVWF: ADVATE at an rVWF: ADVATE ratio of 1.3:1± 0.2 should be administered initially. Subsequent infusions should be with rVWF:RCo 40 to 60 IU/kg with or, in many cases,without 30 to 45 IU/kg ADVATE (only to be administered if plasma FVIII levels fall below 30 IU/L during the treatment period). Dosing may be adjusted downward or upward up to 80 IU/kg rVWF at the treating physician's discretion based upon the subject's prior history, PK and other factors.

If FVIII levels are not available, dosing is at the discretion of the investigator based upon the individual subject's PK data. Using ADVATE (rFVIII, octocog alfa) in addition to rVWF (vonicog alfa) in subsequent doses carries the risk of an excessive rise in FVIII:C. Therefore, reduced doses of ADVATE (rFVIII, octocog alfa) and/or prolongation of the dose interval should be considered.

The following is general guidance and the sponsor's suggestion for treatment of breakthrough bleeds, however each PI will determine the treatment based on the local acceptable practice how to monitor and adjust treatment for a bleeding episode. An effort should be made to discuss with the sponsor (or sponsor's delegate) the treatment strategy.

In general the aim of the initial dose should be full replacement of VWF with VWF:RCo levels of >0.6 IU/ml (60%) and FVIII:C of >0.4 IU/mL (40%). In major bleeding episodes, subsequent doses should keep the trough level of VWF:RCo >50% for 3 days and then as deemed necessary by the investigator for subsequent days. In moderate bleeding episodes, the dose and trough level may be reduced to >30% for as long as deemed necessary by the investigator. Treatment for minor bleeding episodes will generally consist of only 1 or 2 doses of rVWF (vonicog alfa) IP.

If the VWF:RCo level is above 150%, a planned treatment should be delayed by at least 12 hours; if the VWF:RCo level is above 200%, a planned treatment should be delayed by at least 24 hours. In either case, a lower subsequent dose (e.g., 20 IU/kg VWF:RCo) may be appropriate.

Dosing recommendations are listed in Table 3.

Dosage must be individualized based on the subject's weight, VWD type, and the severity of the bleeding episode, as well as on monitoring of appropriate clinical and laboratory measures. In the phase 1 study **070701**, 1.0 IU/kg VWF:RCo raised the circulating level of VWF:RCo by 0.017 IU/mL (1.7 %). In the same study, the observed mean half-life for rVWF (vonicog alfa) was 19.3 hours, with a standard deviation of 10.9 hours.

Table 3
rVWF:RCo Dosing Recommendations for the Treatment of Bleeding Episodes Due to VWD

Classification of VWD	Hemorrhage	Dosage (IU VWF:RCo/kg BW)
Type 1 • Severe (Baseline VWF:RCo activity typically <20%)	Minor (e.g., epistaxis, oral bleeding, menorrhagia[a])	40 to 50 IU/kg (1 or 2 doses)
	Major (e.g., severe or refractory epistaxis, menorrhagia*, GI bleeding, CNS trauma, hemarthrosis, or traumatic hemorrhage)	Initial dose 50 to 75 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment
Type 2 (all variants) and Type 3	Minor (clinical indications above)	40 to 50 IU/kg (1 or 2 doses)
	Major (clinical indications above)	Initial dose of 60 to 80 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment

[a] Menorrhagia is defined as excessive bleeding during menstruation. A diagnosis of menorrhagia will be defined by a prospectively completed Pictorial Blood Assessment Chart (PBAC) score >185 and normal cervical cytology or requiring use of a VWF-containing concentrate for treatment of excessive menstrual bleeding for at least one menstrual cycle during the prior year.

Variances of up to 10% in dosing are permissible during treatment of bleeding episodes, but rounding to the nearest vial size should be avoided.

Subjects with non-neutralizing binding anti-VWF antibodies should initially be treated with a dose known to be efficacious based on the subject's medical treatment history which may differ from the recommendations provided in Table 3. Subjects should be monitored for lack of efficacy as well as for FVIII (mandatory), VWF:RCo (mandatory), and VWF:Ag (optional where testing is not available) levels after 3 to 6 hours. Re-dosing with rVWF (vonicog alfa) in combination with ADVATE (rFVIII, octocog alfa) using the same (initial) dose and adaptation of the dosing frequency should be considered until cessation of the bleed, if the FVIII and/or VWF:RCo levels drop below 30%-50% depending on bleeding severity.

The number of subsequent infusions and the dosage levels prescribed will be determined by the investigator on the basis of the clinical severity, response to current therapy, available laboratory data, and the subject's historical treatment for similar bleeding episodes.

8.6.4.5 Treatment of Surgical Bleeding

Subjects enrolled in this study who require surgery or dental procedures will be treated with IP to manage their surgical bleeding then afterwards will resume their prophylactic rVWF (vonicog alfa) treatment schedule. Subjects who at time of screening have an already scheduled surgical intervention are not eligible for participation in the study.

8.6.4.5.1 Major, Minor and Oral Surgery Definition

The following definitions and criteria are used to serve as a guidance for *major, minor and oral surgery*.

Major surgeries generally refer to major orthopedic surgery (e.g., joint replacement, arthroscopic or open synovectomy, arthrodesis, hardware removals like plates or intramedullary nails, etc.), major abdominal surgery (e.g. open or laparoscopic hernioplasty, cholecystectomy, colon or small bowel resection, etc.), major gynecological surgery (e.g. open or laparoscopic myomectomy, hysterectomy, removal of endometriosis, polyps, cysts, adhesiolysis, etc.), major head and neck surgery (e.g.: tonsillectomy, adenoidectomy, rhinoplasty, lymphadenectomy, thyroidectomy, parotidectomy. etc.), any intracranial , cardiovascular or spinal surgery and any other surgery which has a significant risk of large volume blood loss or blood loss into a confined anatomical space. Extraction of impacted third molars is generally also considered major surgery due to the expected difficulty of surgery and the expected blood loss.

Minor surgeries generally refer to interventions such as placement of intravenous access devices, removal of small skin lesions, arthroscopy, gastroscopy, colonoscopy or conisation.

Oral surgeries comprise extractions of fewer than three teeth, if the teeth are non-molars and have no bony involvement.

A summary schedule of visit assessments and laboratory sampling is included in Supplement tables in Section 20.2.1 and Section 20.3.1.

8.6.4.5.2 Preoperative Priming Dose

12- 24 hours prior to surgery, a priming dose with rVWF (vonicog alfa), using the rVWF IR and $T_{1/2}$ for this subject , will be infused to allow the endogenous FVIII levels to raise to at least 30 IU/dL (minor, oral surgery), or 60 IU/dL (major surgery) at the time of the loading dose of rVWF (vonicog alfa) is infused.

As a general guidance a priming dose of 40-60 IU/kg rVWF:RCo will be administered. If not assessed prior to the preoperative priming dose, a IR recovery may be calculated for subjects undergoing minor and oral surgery.

8.6.4.5.3 Preoperative Loading Dose

An rVWF (vonicog alfa) loading dose should be administed within 3 hours before surgery. VWF and FVIII levels should be assessed within 3 hours prior to surgery initiation and results must be available prior to administering the loading dose. If FVIII levels prior to loading dose administration are not at least 30 IU/dL (minor, oral surgery), or 60 IU/dL (major surgery) ADVATE (rFVIII, octocog alfa) will be administered in addition to rVWF (vonicog alfa) in order to raise FVIII:C levels to recommended levels.

The preoperative loading dose will be calculated as the difference in the target peak and baseline plasma VWF:RCo levels divided by the IR (ΔVWF:RCo x BW (kg) /IR). The PK results will be provided prior to the planned surgery. If the IR is not available, assume an IR of 1.7 IU/dL per IU/kg and calculate the initial dose as follows: (100 − baseline plasma VWF:RCo) x BW (kg) / 1.7. For minor and oral surgery, the IR from the Preoperative Priming Dose visit will be used to guide dosing and the target peak is 50-60 IU/dL VWF:RCo and 40-50 IU/dL FVIII. For major surgery, the target peak is 100IU/dL VWF:RCo and 80-100 IU/dL FVIII.

The surgery may only start after normalization of the activated partial thromboplastin time (aPTT).

8.6.4.5.4 Intra- and Postoperative (maintenance) Dosing

After the preoperative loading dose(s), subjects who have not achieved the desired postinfusion recovery will continue to receive rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) as a bolus infusion, depending on VWF and FVIII levels. The peri- and post-operative substitution regimen will be individualized according to the PK results, intensity and duration of the hemostatic challenge, and the institution's standard of care.

Subjects undergoing minor surgery will be infused with rVWF (vonicog alfa) every 12-24 hours or every other day, targerting ≥30IU/dL (rVWF and FVIII) for at least the first 48 hours.

Subjects undergoing oral surgery will be infused with rVWF (vonicog alfa) at least once within the first 8-12 hours, targeting ≥30 IU/dL (rVWF and FVIII).

Subjects undergoing major surgery will be infused with rVWF (vonicog alfa) every 12-24 hours for at least the first 72 hours post-surgery, targeting a VWF:RCo and FVIII:C trough plasma level >50 IU/dL, followed by further treatment post-72 hours for as long as deemed necessary by the Investigator, targeting a VWF:RCo and FVIII:C trough plasma level of ≥30 IU/dL.

Dose modifications based on pre-infusion VWF/FVIII levels will be performed as needed. For subsequent infusions post surgery, in case pre-infusion levels are not available prior to the consecutive infusion in a timely manner, pre-infusion levels from the previous dose may be used by the investigator for dosing guidance.

Peak plasma level guidance is matching to Section 8.6.4.4.2

A schedule of all perioperative visit assessments and laboratory sampling can be found in supplement tables in Section 20.2.1 and Section 20.3.1.

8.6.4.6 Thrombosis Prophylaxis

Thromboembolic events have been reported in patients who have VWD, especially in the setting of known risk factors for thrombosis including low ADAMTS13 levels. Therefore, subjects who are at risk for developing thromboembolic events should be monitored for early signs of thrombosis, and prophylaxis measures against thromboembolism should be instituted according to current recommendations and standard of care. For all subjects who are VWD patients and are receiving VWF concentrate, attention should be given to avoid exceeding maximal recommended plasma activity levels of VWF:RCo (250 IU/dL) and FVIII (250 IU/dL).

Anticoagulation measures, such as heparin, are acceptable and should follow study site standards. The investigator will record the use and reasons for such measures/agents on the appropriate CRF.

8.6.5 Investigational Product Accountability

The investigator will ensure that the IP(s) is stored as specified in the Pharmacy Manual and that the storage area is secured, with access limited to authorized study personnel. All temperature excursions at the subject's home need to be monitored by the site (please refer to the pharmacy manual). The investigator will maintain records that the IP(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. The IP(s) must be dispensed only at the study site or other suitable location (e.g., infusion center; home, as applicable per study design), as specified in the protocol (see Section 10). Records will be maintained that includes the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

8.7 Source Data

Per ICH E6(R2) on GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). These may be in paper and/or electronic format. Source documents for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

No data will be entered directly onto the CRF.

For additional information on study documentation and CRFs refer to Section 17.2. The use of subject diaries is described in Section 10.5.

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding
   a. Type 1 (VWF:RCo <20 IU/dL) or,
   b. Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2M or,
   c. Type 3 (VWF:Ag ≤3 IU/dL).
2. Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.
3. For on-demand patient group, subject currently receiving on-demand treatment for whom prophylactic treatment is recommended by the investigator.
4. For pdVWF switch patient group, subject has been receiving prophylactic treatmentof pdVWF products for no less than 12 months prior to screening.
5. For on-demand patient group, subject has ≥3 documented spontaneous bleeds (not including menorrhagia) requiring VWF treatment during the past 12 months.
6. Availability of records to reliably evaluate type, frequency and treatment of bleeding episodes during at least 12 months preceding enrollment. Up to 24 months retrospective data should be collected if available. Availability of dosing and factor consumption during 12 months (up to 24 months) of treatment prior to enrollment is required for pdVWF switch subjects and is desired (but not a requirement) for on-demand subjects.
7. Subject is ≥18 years old at the time of screening and has a body mass index ≥15 but <40 kg/m^2.
8. If female of childbearing potential, subject presents with a negative blood/urine pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.[i]
9. Subject is willing and able to comply with the requirements of the protocol.

[i] Refer to Section 20.4 for a list of adequate contraceptive methods for females of childbearing potential.

9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

1. The subject has been diagnosed with Type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD (eg qualitative and quantitative platelet disorders or prothrombin time (PT)/international normalized ratio [INR] >1.4).
2. The subject is currently receiving prophylactic treatment with more than 5 infusions per week.
3. The subject is currently receiving prophylactic treatment with a weekly dose exceeding 240 IU/kg.
4. The subject has a history or presence of a VWF inhibitor at screening.
5. The subject has a history or presence of a FVIII inhibitor with a titer ≥0.4 Bethesda units (BU) (by Nijmegen modified Bethesda assay) or ≥0.6 BU (by Bethesda assay).
6. The subject has a known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins.
7. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
8. The subject has a medical history of a thromboembolic event.
9. The subject is human immunodeficiency virus (HIV) positive with an absolute Helper T cell (CD4) count <200/mm^3.
10. The subject has been diagnosed with significant liver disease per investigator's medical assessment of the subject's current condition or medical history or as evidenced by any of the following: serum alanine aminotransferase (ALT) greater than 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).
11. The subject has been diagnosed with renal disease, with a serum creatinine (CR) level ≥2.5 mg/dL.
12. The subject has a platelet count <100,000/mL at screening.
13. The subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to signing the informed consent.

14. The subject is pregnant or lactating at the time of enrollment.
15. Patient has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
16. The subject has participated in another clinical study involving another IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
17. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
18. The subject is scheduled for a surgical intervention.
19. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
20. The subject has a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
21. The subject is in prison or compulsory detention by regulatory and/or juridical order.
22. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.

9.3 Delay Criteria

1. If the subject has an acute bleeding episode or presents with an acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) the screening visit will be postponed until the subject has recovered.

9.4 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (i.e., reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the termination visit (including cases of withdrawal or discontinuation) are described in Section 10.6 and Section 20.2.

Discontinuation (i.e., complete withdrawal from study participation) may be due to dropout (i.e., active discontinuation by subject) or loss to follow-up (i.e., discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also will be withdrawn from treatment or discontinued from further study participation for the following reasons:

1. The subject is scheduled for an extended treatment period >3 months with non-topical immunomodulating drugs other than anti-retroviral chemotherapy (e.g., α-interferon, corticosteroid agents [equivalent to hydrocortisone greater than 10 mg/day]) during the course of the study.
2. Subjects with chronic hepatitis B or C develop ALT/AST levels exceeding 5 times the ULN for >1 month.
3. Subjects who experience severe hypersensitivity reactions, e.g., anaphylaxis upon exposure to rVWF (vonicog alfa).
4. Subjects who develop a neutralizing inhibitor to rVWF (vonicog alfa) and/or ADVATE (rFVIII, octocog alfa) (biological assays) that results in significant clinical effect, including but not limited to increasing the weekly dose of rVWF by $\geq$ 50%.
5. Subjects who demonstrate clinical signs of thromboembolic events.
6. The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through completion of the pregnancy and up to 1 year post delivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome.
7. The subject begins lactating. IP exposure will be discontinued. The investigator will record a narrative description of the course of the baby's development.
8. The subject is not compliant with the prophylactic treatment regimen and does not adhere to the frequency of IP administration. Once >30% of infusions are missed within a visit interval (3 months), the subject will be discontinued from further participation in the study.
9. The subject repeatedly uses other VWF products for prophylaxis or for the treatment of bleeding episodes in the absence of an acceptable justification to the sponsor.

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient who provides informed consent (i.e., signs and dates the informed consent form) is considered a subject enrolled in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (e.g., 071301) to be provided by the sponsor, 2- or 3-digit number study site number (e.g., 02) to be provided by the sponsor, and 3- or 4-digit subject number (e.g., 0003) reflecting the order of enrollment (i.e., signing the informed consent form). For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 071301-020003. All study documents (e.g., CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The study site is responsible for maintaining a screening log that includes all subjects who provided informed consent. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRF, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

The overall study design is illustrated in the Figure 1. Details on the procedures to be performed at each study visit, including screening, are provided in Supplement 20.2 „Schedule of Study Procedures and Assessments“ and Supplement 20.3 „Clinical Laboratory Assessments“.

10.3.1 Screening Visit

Written informed consent must be obtained from each subject before any study related procedures are performed. To initiate screening procedures, at least 72 hours must have elapsed since the last VWF administration for on-demand subjects and the subject must not be actively bleeding at the time of screening. For switch subjects, the usual interval between their pdVWF prophy infusions must have elapsed since the last VWF administration and the subject must not be actively bleeding at the time of screening. Multimer analysis and VWD gene mutation analysis should be performed at screening if not available in the subject's medical history.

The screening visit will be delayed if the subjects presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like symptoms, inflammatory diseases) until the event has resolved. All screening procedures and confirmation of eligibility shall take place within 42 days prior to the first infusion of IP. If the IP is not infused within 42 days, all screening assessments except blood group, human leukocyte antigen (HLA), genetics, multimeric pattern and [redacted], must be repeated to reconfirm eligibility. Refer to Supplement 20.2 and Supplement 20.3. Upon completion of screening procedures, subject eligibility will be confirmed by the sponsor on a subject eligibility form before additional study procedures are undertaken. The subject will maintain a diary that will include infusion logs (see Section 10.5). The allocation of IP will be initiated after the subject has qualified for home treatment (see Section 8.6.4.3.2).

In the event of a subject experiencing a bleeding episode that requires treatment between the screening visit and the subsequent visit (i.e. initial PK assessment visit for on-demand subjects or prophylaxis initiation visit for switch subjects), the subject will be treated with rVWF (vonicog alfa). If rVWF (vonicog alfa) is not available for any reason, e.g., subject not yet trained on IP administration, study site visit for IP administration not feasible, etc., the subject may use his/her standard of care, such as commercial pdVWF/FVIII products, and the reason for the use of non-IP products should be clearly documented.

10.3.2 Baseline Visit – Initial PK Assessment (On-demand Subjects Only)

After screening and confirmation of eligibility on-demand subjects will undergo an initial PK assessment. Subjects will receive a dose of 50 ± 5 IU/kg rVWF:RCo to determine VWF and FVIII levels. 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). See Section 20.2 and Section 20.3. IP infusion vials from the same lot number should be used for all PK-assessments per subject. Samples for measurement of FVIII and VWF activity taken through to 6 hours post-infusion will be obtained from an extremity different from that used for the infusion of IP. Where needed, the phlebotomy site will be kept patent via an infusion of normal saline. In this event, at least 5 mL of blood will be collected and discarded before collection of the next test sample into a fresh syringe.

If the subject has a central venous catheter, the central line should be used to administer the infusion and a peripheral venipuncture should be used to collect the blood samples.

In the event that a blood sample must be drawn through the central line used for administration of IP, the line must first be flushed with at least 10 mL normal saline or other suitable catheter flush solution that does not contain anticoagulant. At least 5 mL of whole blood must be collected and discarded prior to obtaining the sample.

If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.6.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment.

For pdVWF switch subjects, PK profile will not be assessed until reaching steady state after initiation of prophylaxis (see Section 10.3.4).

10.3.3 Prophylaxis Initiation Visit

The prophylaxis initiation visit will occur after the blood sample for the 96 hour PK assessment is drawn for on-demand subjects or within 42 days after screening and confirmation of eligibility for pdVWF switch subjects. The subject will receive the first rVWF (vonicog alfa) prophylactic dose of rVWF: RCo. Details on dose are provided in Section 8.6.4.3.

Procedures and assessments at this visit include (but are not limited to): AEs, bleeding episodes, medications taken, and non-drug therapies. Within 2 hours prior the IP infusion, a physical examination will be performed. Vital signs will be assessed within 30 minutes prior to IP rVWF (vonicog alfa) infusion and 30 minutes ± 15 minutes after IP infusion. Further details are provided in Supplement 20.2 and Supplement 20.3.

10.3.4 Initial Steady State PK-Assessment (pdVWF switch subjects only)

For pdVWF switch subjects, a full PK profile will be assessed at steady state conditions on two occasions. The initial PK assessment will be performed shortly after reaching steady state after starting prophylaxis dosing, which is suggested after 11 days post the 1st, around prophylaxis dose #5-6. The 2nd PK assessment at steady state will be performed at the end of the study.

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). In case the dosing schedule does not permit the 96 hr sampling, this sampling time point can be omitted (See Section 11.6). IP infusion vials from the same lot number should be used for all PK-assessments per subject.

Samples for measurement of FVIII and VWF activity taken through to 6 hours post-infusion will be obtained from an extremity different from that used for the infusion of IP. Where needed, the phlebotomy site will be kept patent via an infusion of normal saline. In this event, at least 5 mL of blood will be collected and discarded before collection of the next test sample into a fresh syringe.

If the subject has a central venous catheter, the central line should be used to administer the infusion and a peripheral venipuncture should be used to collect the blood samples. In the event that a blood sample must be drawn through the central line used for administration of IP, the line must first be flushed with at least 10 mL normal saline or other suitable catheter flush solution that does not contain anticoagulant. At least 5 mL of whole blood must be collected and discarded prior to obtaining the sample.

If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.6.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment. In case of surgery or bleeding, the PK assessment should be performed after 11 days after 1st prophylactic dose after re-start of prophylactic regimen. See section 11.6 for more details.

10.3.5 Treatment of Bleeding Episodes

Treatment of bleeding episodes is described in detail in Section 8.6.4.4 and treatment of perioperative bleeding is described in detail in Section 8.6.4.5.

10.3.6 Perioperative Visits (only applicable if surgery is needed)

The perioperative visits from priming dose through postoperative day 14 will be required to check daily intra- and postoperative weight-adjusted dose of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa). Details on the procedures and assessments performed at each visit can be found in supplement tables in Section 20.2.1 and Section 20.3.1.

10.3.7 Follow-Up Visits (1 Month ± 1 Week, 2 Months ± 1 Week, 3 Months ± 2 Weeks, 6 Months ± 2 Weeks, 9 Months ± 2 Weeks post Prophylaxis Initiation Visit)

Visits will be performed after the prophylaxis initiation visit at 1 month ± 1 week, 2 months ± 1 week, and 3 months ± 2 weeks and thereafter every three months ± 2 weeks. Additional visits may occur if clinically indicated (see Section 10.3.8).

When possible, site visits should be scheduled on days when the subject is expected to infuse rVWF (vonicog alfa). Within 2 hours prior to the rVWF (vonicog alfa) IP infusion, a physical examination will be performed. Vital signs will be assessed within 30 minutes prior to IP infusion and 30 minutes ± 15 minutes after IP infusion. Incremental recovery (IR) will be determined at each follow-up visit based on VWF:RCo activity assessed prior to and after IP infusion.

The blood sample for IR analysis will be drawn within 30 minutes prior to IP infusion and 30 minutes ± 5 minutes after IP infusion. rVWF (vonicog alfa) will be infused at the regular prophylactic dose. For each subject's recovery analysis IP infusion, vials from the same lot number should be used.

Testing for VWF:RCo VWF:CB, rVWF:Ag, and FVIII:C level will be performed using the blood sample obtained before and after IP infusion.

The blood sample prior to IP infusion will also be used for the assessment of neutralizing and binding antibodies, clinical chemistry and hematology. For on-demand subjects, a washout period of at least 72 hours after the last infusion applies before the blood draw for the immunogenicity assays. For switch subjects, the wash out period may be reduced to the time interval between their pdVWF prophy infusions Bleeding episodes and the hemostatic efficacy will be evaluated based on the review of the patient diary. See Section 20.2 and Section 20.3. The evaluation of IP consumption and treatment compliance will be performed based on subject's diary entries. If a subject is not compliant with the prophylactic treatment regimen and does not adhere to the required frequency of administration of IP infusions (>30% of infusions were missed within a visit interval [3 months]) the subject will be withdrawn from the study.

At the 6 months ± 2 week visit an ECG will be performed and [redacted] data will be collected.

For the hemostatic efficacy assessment the following information will be recorded by the subject in the patient diary: bleeding location, type, severity, onset and resolution date and time, infusion date and time, clinical efficacy according to the rating scale. If at any time during the study a subject's bleeding episode does not adequately respond to rVWF (vonicog alfa) therapy, he/she will be evaluated for the presence of neutralizing and total binding antibodies. Refer to Section 12.9.3.2.

Further guidance on completing the subject's diary will be provided to the subjects during training for home treatment (see Section 8.6.4.3.2).

10.3.8 Unscheduled Visits

For any unscheduled visit (except for collection of IP) a clinical assessment will be performed as per the scheduled follow-up visits with the exception of [redacted], ECG, and IR determination (refer to Supplement 20.2 and Supplement 20.3).

Subjects who have more than one bleeding episode in 3 months, or an increased frequency of bleeding, should go to the study site for an unscheduled visit.

Follow-up visits after the subject has experienced a bleed may be requested by the investigator. Additional assessments may be required which are at the discretion of the investigator.

10.3.9 End of Study PK Assessment and Study Termination Visit (12 Months ± 2 Weeks post Prophylaxis Initiation Visit)

At the 12 month ± 2 week visit, a full PK analysis at steady state will be performed for both cohorts: on-demand and switch subjects. 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) unless dosing schedule does not permit, in which case the 96 hr sampling can be omitted. If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.6.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment and the PK assessment should be performed after 11 days after 1st prophylactic dose after re-start of prophylactic regimen. See section 11.6 for more details.

Refer to Supplement 20.2 and Supplement 20.3 for the other assessments to be performed at the PK assessment and study completion visits.

For on-demand subjects, a washout period of at least 72 hours is required between the PK infusion and the study termination visit (at the time of the 96 hour postinfusion PK assessment). For switch subjects, the wash out period may be reduced to the time interval between their rVWF (vonicog alfa) prophy infusions.Refer to Supplement 20.2 and Supplement 20.3 for the list of assessments to be performed at the termination visit.

Subjects will be offered the option to continue to receive rVWF (vonicog alfa) in a long-term continuation study.

10.4 Medications and Non-Drug Therapies

The following medications and non-drug therapies are **not** permitted within 30 days before study entry and during the course of the study:

Medications:

- 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) and an extended treatment period >3 months.
- Another investigational and/or interventional study drug (except rVWF and FVIII administered under the surgery protocol).

A subject who has taken any of these medications or received any of these non-drug therapies during the study will be withdrawn from the study.

The following medications are permitted during the course of the study:

- Antifibrinolytics (e.g., tranexamic acid, ε-amino caproic acid) or topical hemostats as needed, according to each institution's standard of care. These may be used, in accordance with local standard clinical practice, as the initial or only treatment for minor and moderate bleeding events. However, if the bleeding has not stopped within 24 hour following administration of this non-VWF treatment, infusion(s) with rVWF (vonicog alfa) should be started per protocol
- Emergent use of a VWF concentrate other than rVWF (vonicog alfa) may be permissible under certain circumstances (see Section 8.6.4.4.1)

Details of all adjunctive hemostatic medication used, including dose and reason for use, must be recorded in the eCRF.

10.5 Subject Diary

1. An electronic subject diary will be provided to each subject at the screening visit to record the following information:
    - IP infusions to include date, start and stop times of the infusion, number of vials utilized, and infusion volume for prophylactic treatment or treatment of spontaneous and traumatic bleeding episodes
2. Details of bleeding episodes (site, type, severity and date/time of bleeding) and response to treatment as described in Section 8.6.4.4
3. Subjective hemostatic efficacy assessments

4. Untoward events/unwanted experiences

5. Concomitant medications (including immunizations) and non-drug therapies

6. Patient Reported Outcomes (PROs)

Subjects and/or their legally authorized representatives will be trained on use of the diary. The diary will be provided in electronic format and remain with the subject for the duration of the study. The investigator will review the diary for completeness and request missing information periodically and in a timely manner. The investigator will record/capture any unwanted experience reported by the subject which may qualify as an AE on the AE eCRF.

Infusions performed at the study site will first be recorded in the site's source documents and not in the patient diary.

Subject entries in the diary will serve as source records. During study participation the investigator has access to the database holding the subject diary data. After study closure, the investigator will receive the diary records for their subjects, including audit trail records, in PDF format. The data will be transmitted to the CRF by a validated transfer.

Paper diary may be utilized in rare case where electronic diary use is not possible.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have completed all study procedures according with the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, AE (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, e.g., technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the study termination visit. If the termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the termination visit.

If a subject terminates participation in the study and does not return for termination visit, his/her last recorded assessments shall remain with the last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.2 Schedule of Study Procedures and Assessments and Supplement 20.3 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

10.7 Procedures for Monitoring Subject Compliance

Subject compliance with the procedures of this study (treatment regimens and study visits) will be monitored by the investigator or a licensed healthcare professional at the study site.

During the regular scheduled follow-up visits a direct review of the subject's source data (e-diaries) will be performed at the sites and evaluated against the protocol requirements. In addition drug accountability will be evaluated at each follow-up study visit and the study termination visit by comparing the infusions recorded in the subject diary with empty vials returned by each subject to the study site, and the study site's dispensing record. Protocol deviations will be noted in the final report.

11. ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

11.1 Assessment of Spontaneous Bleeding Episodes/Annualized Bleed Rate

The annualized bleed rate (ABR) will be assessed based upon each individual spontaneous bleed, requiring coagulation factor replacement therapy, i.e., rVWF (vonicog alfa) treatment. The following details on bleeding episodes will be recorded by the subject in the electronic diary (for home treatment), the subject's healthcare provider in the site's source documents (for treatments away from the primary investigative site), or by authorized, qualified personnel at the participating site in the subject's medical records (for hospital-based treatment):

- Location of bleed; i.e., joint, menorrhagia, epistaxis, gastrointestinal, soft tissue, muscle, body cavity, intracranial, etc.
- Type of bleed; i.e., spontaneous, traumatic, unknown
- Severity of bleed; i.e., minor, moderate, and major (see Table 3)
- Date and time of onset of bleed
- Date and time of each infusion of rVWF (vonicog alfa) or rVWF (vonicog alfa)-ADVATE (rFVIII, octocog alfa) used to treat a bleeding episode
- Date and time of resolution of the bleeding episode

Study site personnel are qualified after they have undergone training during the qualification of the site.

All types of bleeds, including traumatic bleeds, will be recorded. Bleeding episodes should be organized by where they occur in addition to whether they occurred spontaneously or due to a traumatic event.

Bleeds occurring at the same anatomical location (e.g., right knee) with the same etiology (i.e., spontaneous versus injury) within 24 hours after onset of the first bleed will be considered a single bleed. Bleeding occurring at multiple locations related to the same injury (e.g., knee and ankle bleeds following a fall) will be counted as a single bleeding episode.

All efforts should be made to use rVWF (vonicog alfa) for treatment of bleeding episodes. If needed, the use of a VWF concentrate other than IP for the treatment of bleeding episodes will not disqualify the subject from further participation in the study.

11.2 Evaluation of ABR Before rVWF Prophylaxis and ABR Under rVWF Prophylactic Treatment

At screening, the subject's medical history will be recorded, including the number and location of all spontaneous and traumatic bleeding episodes within the past 12 months (up to 24 months if available). The maximum interval of bleed-free periods as well as trauma induced bleeding episodes will also be recorded (prospectively and retrospectively).

11.3 Number of Infusions and Total Weight Adjusted Consumption of rVWF and ADVATE and historical prophylaxis dosing and factor consumption during pdVWF prophylaxis treatment prior to enrollment

The number of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) (in case of bleeding episode treatment) infusions will be logged in the subject diary. Based on these entries the weight adjusted consumption will be calculated.

At the screening, historical pdVWF dosage and dosing frequency during 12 and up to 24 months of pdVWF prophylactic treatment prior to enrollment will be recorded for the pdVWF switch subjects in order to calculate the consumption of pdVWF.

11.4 Assessment of Efficacy for Treatment of Bleeding Episode

Investigators will be asked to assess and record hemostatic efficacy after resolution of each bleeding episode using the 4-scale rating system outlined in Table 4.

Table 4
Efficacy Rating Scale

Rating	Efficacy Rating Criterion	
	Minor and Moderate Bleeding Events	**Major Bleeding Events**
Excellent (=1)	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF containing coagulation factor containing product required	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF containing coagulation factor containing product required
Good (=2)	1-2 infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required	< 1.5 x infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required
Moderate (=3)	3 or more infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required	≥ 1.5 x infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required
None (=4)	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF containing coagulation factor containing product required	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF containing coagulation factor containing product required

11.5 Assessment of Efficacy for Treatment for Surgical Bleeding

For those undergoing surgery, the operating surgeon will be asked to assess and record actual versus predicated blood loss and intraoperative hemostatic efficacy immediately after surgery.

The investigator will be asked to assess and record an overall assessment of hemostatic efficacy 24 hours after the last perioperative rVWF (vonicog alfa) infusion or at day 14 post-operation, whichever occurs first, using the 4-scale rating system described in Table 5.

Table 5
Assessment of Hemostatic Efficacy

Rating	Overall Assessment of Hemostatic Efficacy 24 Hours After the Last Perioperative rVWF Infusion
Excellent (1)	Intra- and post-operative hemostasis achieved with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) was as good or better than that expected for the type of surgical procedure performed in a hemostatically normal subject
Good (2)	Intra- and post-operative hemostasis achieved with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) was probably as good as that expected for the type of surgical procedure performed in a hemostatically normal subject
Moderate (3)	Intra- and post-operative hemostasis with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) was clearly less than optimal for the type of procedure performed but was maintained without the need to change the rVWF (vonicog alfa) concentrate
None (4)	Subject experienced uncontrolled bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of rVWF (vonicog alfa) concentrate

11.6 rVWF Pharmacokinetics and Pharmacodynamics

PK will be assessed twice for all subjects.

For on-demand subjects, an initial PK assessment using a dose of 50 IU ± 5 IU/kg rVWF:RCo will be performed at the baseline visit, and 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 week 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 assay. 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 assessment using the subject's individualized dose will be performed shortly after reaching steady state, which is estimated to be reached for the majority of subjects after approximately 11 days from the 1st prophylactic dose. To fit any logistical requirements, samples for PK analysis can be taken after prophylaxis dose #5-6, and whenever possible, sample collections should be during the longer partial interval of the alternating irregular dosing intervals. For example, if a subject follows a dosing regimen as follows:

Date	Weekday	Dose number	Interval	Time from 1st 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 profile will be assessed at the end of the study, i.e. 12 month ± 2 week visit with a PK 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 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). If the dosing interval for a certain switch subject wouldn't allow for the full 11 post-infusion timepoints sample collection, 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 for an individual switch subject.

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

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

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, whether or not considered causally related to the IP.

12.1.1.1 Serious Adverse Event

An SAE is defined as an untoward medical occurrence that, at any dose, meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are (including but not limited to):
  - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
  - Reviewed and confirmed seroconversion for HIV, hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)

- Development of clinically significant neutralizing VWF antibodies
- Development of neutralizing antibodies to FVIII (titer ≥0.4 BU [by Nijmegen- modified Bethesda assay] or ≥0.6 BU [by Bethesda assay])
- Thromboembolic events (e.g., myocardial infarction, stroke, transient ischemic attack [TIA], deep vein thrombosis [DVT] or pulmonary embolism)
- Hypersensitivity reactions (e.g., anaphylaxis [for definition, refer to Section 12.6.2] and other immediate and delayed hypersensitivity reactions which may manifest with urticarial rash, pruritus, flushing, angioedema of the face, extremities, or laryngeal tissues [leading to throat tightness with stridor], wheezing, gastrointestinal symptoms, and/or hypotension)

Uncomplicated pregnancies, following maternal or paternal exposure to IP are not considered an AE/SAE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE and should be reported per SAE reporting guidelines provided in Section 12.1.2.3 (Safety Reporting).

12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any suspected adverse reaction to study treatment that is both serious and unexpected is considered a SUSAR.

The event(s) must meet all of the following:

- Suspected adverse reaction (which implies that there is reasonable evidence indicating a causal relationship between the event and the study treatment),
- Unexpected (per Reference Safety Information (RSI)/IB), and
- Serious

Once determined to meet the criteria for a SUSAR, the sponsor will ensure expedited SUSAR reporting is completed in line with the regulatory requirements in participating countries as outlined in the Safety Management Plan.

12.1.1.3 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet any of the seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) listed in section 12.1.1.1.

12.1.1.4 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (e.g., IB, PI [prescribing information]). "Unexpected" also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.1.1.5 Preexisting Disease

Preexisting diseases that are present before entry in to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described as "worsening" of the pre-existing condition on the AE CRF.

12.1.2 Assessment of Adverse Events

For the purposes of this study, the following will not be considered as AEs and will not be included in the analysis of AEs.

- Bleeding episodes are part of the underlying disease and therefore are not AEs; they will be evaluated in the context of efficacy.
  - For non-serious bleeding episodes caused by an injury, the injury would not be reported as an AE, unless it resulted in a medical finding other than a bleeding episode (e.g., abrasion of skin). Therefore, any VWD-related bleeding event (e.g., epistaxis, gastrointestinal bleeding, musculo-skeletal bleeding, menorrhagia) that is non-serious will not be reported as an AE. However, the investigator may decide that the event is an AE if the event also would have occurred in a healthy individual under the same circumstances.
  - For serious bleeding episodes (bleeding SAEs): Bleeding events that meet seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) should be captured on the SAE eCRF and reported as an SAE to the Sponsor or designee (e.g., CRO) on an SAE Report form as described in Section 12.1.2.3 (Safety Reporting).
- Seroconversion after documented HAV/HBV vaccination prior to or during the study period.

Each AE from the first IP exposure to the study completion date will be described on the AE CRF using the term representing medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial verbatim expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2

For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable, action taken with regards to the study treatment (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution or until the subject's condition returns to the level at the baseline for pre-existing conditions.

If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the protocol-specified dosage (including underdosing /overdosing [<20 IU/kg rVWF:RCo or >100 rVWF:RCo], abuse, and withdrawal, treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after administration of IP will be reported on a Pregnancy Form and followed-up at 1 year post-delivery, if feasible.

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the SAE Form within 24 hours after awareness: no additional reporting on CRFs is necessary.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, e.g., assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs

- Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP, is not biologically plausible per mechanism of action of the IP, or has a much more likely alternative etiology).

- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of IP
  - An alternative etiology is equally or less likely compared to the potential relationship to the IP
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
    - Reappearance of a similar reaction upon re-administration (positive re-challenge)
    - Positive results in a drug sensitivity test (skin test, etc.)
    - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
  - Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within 5 days after IP infusion, the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

12.1.2.3 Safety Reporting

AEs and SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Section 20.2) and Section 12.1.2.

Adverse Events and SAEs are to be recorded on the AE page of the eCRF. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the IP, must be reported immediately (within 24 hours of the study center's first knowledge of the event). All SAEs must be reported in English via the Electronic Data Capture (EDC) system by completing the relevant eCRF page(s) and also by SAE Report Form via fax/email to Sponsor's Global Drug Safety (Baxalta GDS) department within 24 hours of becoming aware of the event for SAEs (for contacts, instructions, and additional details, refer to the SAER form).

Within 24 hours of site awareness of a SAE (or Pregnancy) study sites will complete and send all SAE (or Pregnancy) reports to a dedicated:

Baxalta Global Drug Safety fax number: [redacted]

OR

email: [redacted]

The responsible Site Monitor will review the SAE (or Pregnancy) Reports for completeness, will reconcile the reports against the EDC database, and will follow-up with sites to obtain missing information and/or information requiring clarification. Any SAE associated with a pregnancy must be reported on the SAER Form.

For Follow-up Reports, the site shall use a new SAER form (marked as Follow-up) and the new information should be entered together with a brief narrative identifying the updated data.

An SAER should include the following minimum information:

1. Protocol Number (on all pages)
2. Subject identification number (on all pages) and demographics (gender, age at onset of event and/or date of birth)
3. Investigational product and treatment regimen (including date of the first dose of IP, date of the last dose of IP prior to the onset of the SAE)
4. Medical Term for Event (Diagnosis preferably)
5. Description of the SAE, including:
    - Date of onset
    - Causal relationship assessment by the Investigator
6. Seriousness criteria (e.g., death, life-threatening, hospitalization, medically significant, or other criterion)
7. Name, address, fax number, email, and telephone number of the reporter/Investigator

Post-trial SAE Reporting: In compliance to EudraLex Volume 10 (Clinical trials guidelines, Chapter II: Safety Reporting from the European Commission), which references an EMA guidance (ICH Topic E 2 A - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting), clinical sites/the investigator should report to the Sponsor SAEs after a subject´s study completion. Study sites will be provided a Post-Trial SAER form to complete and report these post-study SAEs to the Sponsor within the 24 hours of their awareness. Site Monitor will instruct the site that any such Post-Trial SAEs should be reported on the study-specific Post-Trial SAER form if/when the site becomes aware of it. Such information will not be actively monitored by the sponsor after completion of the study.

These events shall be reported to Baxalta GDS who will process them in the same way as SAEs occurring during the study. Post-Trial SAEs do not need to be captured in the study EDC database if it is already locked. Irrespective if captured in the EDC database or not, such Post-Trial SAEs will become part of the GDS database. The monitor should remind the clinical site about the post-trial SAE reporting requirements during interim monitoring visits, upon each subject's study completion as well as during the close-out visit.

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of the clinical trial
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor.
In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committees (ECs) and relevant competent authority(s) are notified of the urgent measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (i.e., from the time of signed informed consent up to but not including the first IP exposure) will be described on the SAER. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE.** NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g. reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (e.g., potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) 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. The subject's medical history will also include documented history of on-demand or pdVWF prophylaxis treatment for at least the past 12 months and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 months (up to 24 months if available).

All medications taken and non-drug therapies received in the 2 weeks prior to study entry and all concomitant medications and non-drug therapies during study will be recorded on the CRFs.

Data on medical history, drug and non-drug therapy history of those subjects who transition from surgery rVWF (vonicog alfa) study will be used from the eCRF of the main studies, will be updated, if applicable, and transcribed into the respective eCRF of the prophy study.

12.6 Physical Examinations

At screening and subsequent study visits (as described in Section 10.3), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 12.1.1.5), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.6.1 Thromboembolic Events

There is a risk of occurrence of thrombotic events, particularly in patients with known clinical or laboratory risk factors for thrombosis including low ADAMTS13 levels. Therefore, patients at risk must be monitored for early signs of thrombosis during the study and prophylaxis measures against thromboembolism should be instituted according to current recommendations and standard of care. Additional diagnostic procedures are required according to each institution's standard of care which may consist of, but are not limited to the following:

- For DVT: Magnetic Resonance Imaging (MRI), compression ultrasound or impedance plethysmography.
- For pulmonary embolism: ECG, chest radiography, perfusion/scintiscan or MRI.
- For myocardial infarction: ECG, cardiac enzymes, echocardiography
- For stroke: diffusion-weighted magnetic resonance imaging or computed tomography, ABCD scoring, carotid imaging

Results of diagnostic procedures may be forwarded to the sponsor to be reviewed by an independent external expert panel, such as the DMC, if applicable.

12.6.2 Anaphylaxis

The diagnosis of anaphylaxis is highly likely when any of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g, generalized urticaria, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:
   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin or mucosal tissue (e.g., generalized urticaria, pruritus or flushing, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to a known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP

If a subject develops anaphylaxis in the course of the clinical study, this needs to be reported as SAE (Section 12.1.1.1). Additional blood will be drawn for Anti-VWF IgE antibody testing (Section 12.9.13).

12.7 Vital Signs

Vital signs will be assessed pre- and post-infusion at each visit, if not stated otherwise:

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

Vital signs (pulse rate, respiratory rate, and blood pressure) should be recorded within 30 min before and after IP administration. The assessment of vital signs per planned study visit is outlined in Supplement 20.2.

Vital sign values are to be recorded on the physical examination eCRF. For each vital sign value, the investigator will determine whether the value is considered an AE (see definition in Section 12.1). If assessed as an AE, the medical diagnosis (preferably), symptom, or sign, will be recorded on the AE eCRF. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE, should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.8 Electrocardiogram

A standard 12-lead ECG at rest will be performed at screening, at the 6 month follow-up visit and at the study termination visit and evaluated for medical significance by the investigator.

12.9 Clinical Laboratory Parameters

Refer to the Laboratory Manual for information on collection and processing of samples.

In general all laboratory tests will be performed at central laboratories, except the pregnancy and blood group test which will be performed at the local laboratory. In addition, relevant critical safety laboratory tests for complete blood count (CBC), serum chemistry and/or coagulation parameters such as VWF and FVIII activity may also be performed in the local laboratory to ensure that results will be available immediately to the investigator. In principle, results from the central laboratory will be used for data analysis purposes. The assays performed in the central laboratories are specified in the Laboratory Manual. The investigator will supply the sponsor with a list of the normal ranges and units of measurement for the laboratory variables to be determined at the site. Laboratory values such as antibodies to other proteins are not required immediately and will be assessed later during the course of the study.

Any abnormal laboratory value that is considered clinically significant by the investigator based on a local laboratory test result (reference range and the units to be provided) should be confirmed by a central laboratory test result for which the sample is drawn/collected within 24 hours of the abnormal finding by the local laboratory.

12.9.1 rVWF Pharmacokinetics and Pharmacodynamics

Details on pharmacokinetic and pharmacodynamics assessments are provided in Section 11.6.

12.9.2 Hematology and Clinical Chemistry

The hematology panel will consist of CBC [hemoglobin, hematocrit, erythrocytes (ie, red blood cell count [RBC]; mean corpuscular volume [MCV], mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration [MCHC]), and leukocytes (i.e., white blood cell count [WBC])] with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.

The clinical chemistry panel will consist of sodium (Na), potassium (K), chloride (Cl), ALT, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase (AP), blood urea nitrogen (BUN), CR, and glucose (Glu).

Blood will be obtained for assessment of hematology and clinical chemistry parameters at screening, during PK-assessment prior to rVWF (vonicog alfa) IP infusion, after 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours post rVWF (vonicog alfa) IP infusion, at all follow-up visits as per schedule (refer to Supplement 20.3 Clinical Laboratory

Assessments), i.e., 4 weeks ± 1 week, 8 weeks ± 1 week and every 3 months ± 2 weeks, and at study completion. Hematology and clinical chemistry assessments will be performed on Ethylenediaminetetraacetic acid (EDTA)-anticoagulated whole blood and serum, respectively, at the central laboratory.

12.9.3 Immunology

12.9.3.1 Antibodies to VWF and FVIII

All subjects will be tested for binding and neutralizing antibodies to VWF and FVIII at screening, at initial PK assessment, at each of the scheduled follow-up visits and at the study completion visit. Testing will be done prior to IP infusion and with at least a 72 hour wash out period since the last IP infusion. If there is any suspicion of inhibitor development (e.g. excessive bleeding) binding and neutralizing antibodies to VWF and FVIII may be tested at the discretion of the investigator.

12.9.3.2 Neutralizing and Total Binding Anti-VWF Antibodies

The assays to establish the presence of neutralizing and total binding anti-VWF antibodies have been established in the absence of international standards and with only limited numbers of positive controls. Therefore, caution is advised in interpreting positive results. In particular, any clinical association, changes in the natural history of the disease, effect of therapy, etc. needs to be taken into account for final judgment. The sponsor's Medical Director should be consulted for additional advice. As part of the AE follow-up, any sample testing positive needs to be confirmed after 2-4 weeks for central laboratory testing. Only confirmed neutralizing anti -VWF antibodies are considered inhibitors (see Section 12.9.3.4). These subjects need to be closely monitored and therapy adjusted accordingly.

12.9.3.3 Binding antibodies to VWF

The presence of total binding anti-VWF antibodies will be determined by an enzyme-linked immunosorbent assay (ELISA) employing polyclonal anti-human Immunoglobulin (Ig) antibodies (IgG, IgM and IgA). For this assay (ELISA), recombinant human VWF will be coated onto a microtiter plate, then incubated with dilutions of the positive control, the negative control or test sample. Antibodies against human VWF that are present in the samples bind to the coated antigen and will be detected with a horseradish peroxidase (HRP)-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a human monoclonal antibody specific for human VWF spiked into the negative control. The negative control for this assay is pooled normal human plasma.

Plasma samples are analyzed for binding antibodies against the specific antigen in two steps. First, the sample is screened for antibodies and the titer of binding antibodies is determined. Second, the specificity of positive antibody results is confirmed.[16]
In brief, all samples are serially diluted (initial dilution 1:20 and further diluted 1:2).

The titer endpoint, defined as the highest dilution that still gives a positive signal above cut off level, is determined in two independent duplicates. The cut off level is established based on background signal level of healthy plasma donors (n=160) and set to include 5% false positives to be as sensitive as possible (95% percentile). The ELISA assay is validated allowing an assay variability of ± 1 titer step. Therefore, differences ≤ 2 titers steps may be due to variability of the ELISA assay. Specificity has to be confirmed in a competition assay when a sample has a titer of 1:80 or higher in the screening assay. Based on the validation criteria samples tested in the screening assay at 1:20 or 1:40 cannot be confirmed in the competition assay. A positive screening value is confirmed if the difference between the titers determined for the subject sample (re-screen) and for the subject sample with pre-incubation (confirmation sample) is > 2 titer steps. Antibody titers of subject samples will only be reported as positive, if the results of the screening and confirmatory analysis fulfill these acceptance criteria. The titer to be reported is always the one determined in the original screening procedure (independent of the result of the re-screening in the confirmation procedure).

A more detailed test procedure will be supplied upon request or pro-actively if a sample tests positive. A treatment related increase of the binding anti-VWF antibodies is expected, if the titer increases by more than 2 titration steps. These subjects need to be closely monitored and therapy adjusted accordingly.

12.9.3.4 Neutralizing Antibodies to VWF

Three functional VWF assays, VWF:CB, VWF:RCo and VWF:FVIIIB assays, will be used to test for the presence of neutralizing anti-VWF antibodies. Neutralizing antibodies to VWF:RCo, VWF:CB and VWF:FVIIIB activities will be measured by assays based on the Bethesda assay established for quantitative analysis of FVIII inhibitors (Nijmegen modification of the Bethesda assay).[17] The amount of inhibitor is expressed as BU per mL. One BU is thereby defined as the amount of inhibitor that decreases the measured activity in the assays to 50% of that of the negative control samples. The assays were validated using human plasma samples from two type 3 VWD patients with low (1-2 BU/mL) and high (~10 BU/mL) titer inhibitors and plasma samples from non-human primates immunized with human rVWF (vonicog alfa) (>100 BU/mL).

If a subject has a measurable baseline level of VWF activity in the respective assay, it is taken into account in the calculation of the residual activity. However, if baseline levels are too high (>15% VWF:RCo), inhibitors may not be reliably detected.

To exclude false positive results, the detection limit for anti-VWF inhibitors was set to 1 BU/ml for all 3 assays. The rationale for this cut-off value is the relatively high CI of the underlying assays, making determinations at the end of the evaluation range of the Bethesda reference curve uncertain.[18] A more detailed test procedure may be requested to further characterize the anti-VWF inhibitors, if detected.

Only confirmed positive anti-VWF inhibitor test result will be reported and will be considered as a medically significant SAE.

12.9.3.5 Binding Antibodies to FVIII

Binding antibodies against FVIII will be analyzed using a proprietary enzyme immunoassay. The testing strategy will be as described for binding anti-VWF antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.3.6 Neutralizing Antibodies (Inhibitors) to FVIII

Neutralizing antibodies (inhibitors) to FVIII will be assessed by the Nijmegen modification of the Bethesda assay in a central laboratory. To verify a FVIII inhibitor, additional testing (such as tests for Lupus anticoagulants) may be initiated. Positive FVIII inhibitor tests will be defined as $\geq$ 0.4 BU by the Nijmegen-modified Bethesda assay that is confirmed by a second test performed on an independent sample obtained 2-4 weeks following the first test. Only confirmed positive FVIII inhibitor test result will be reported.

12.9.4 Antibodies to Other Proteins

Plasma will be assayed for the presence of antibodies against CHO protein (total Ig), murine IgG and human Furin (total Ig) using proprietary enzyme immunoassays. The testing strategy will be as described for binding anti- VWF antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.4.1 Anti-CHO Protein

Total Ig antibodies (IgG, IgA, IgM) against CHO protein will be analyzed. For this assay (ELISA), CHO protein derived from cultures of untransfected cells and propagated under the identical cell culture conditions used for ADVATE (rFVIII, octocog alfa) production will be coated onto a microtiter plate, then incubated with dilutions of the positive control, negative control or test sample. Antibodies against CHO protein that are present in the samples bind to the coated antigen and will be detected with a HRP-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a polyclonal goat anti-CHO protein antibody spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.4.2 Anti-Murine IgG

A commercially available ELISA (Medac, Hamburg, Germany) will be used to detect and to quantify IgG antibodies originating from human plasma that are directed against mouse-IgG (HAMA: human anti- mouse antibodies). Microtiter plates coated with mouse IgG will be incubated with dilutions of the standard, the positive control, the negative control or the test sample. Antibodies against mouse IgG that are present in the samples bind to the coated antigen and form a bridge to a peroxidase coupled mouse IgG antibody that will be used for detection (bridging format of the ELISA assay). The positive control for this assay will be a polyclonal goat anti-murine IgG spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.4.3 Antibodies to Human Furin

Total Ig antibodies (IgG, IgA, IgM) against human Furin will be analyzed. For this assay (ELISA), recombinant human Furin will be coated onto a microtiter plate, then incubated with dilutions of the positive control, the negative control or test sample. Antibodies against human Furin that are present in the samples bind to the coated antigen and will be detected with a HRP-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a human monoclonal antibody specific for human Furin spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.5 Viral Serology

The following viral seromarkers will be assessed at screening:

- HIV: anti-HIV 1, HIV 2
- HAV: anti-HAV (IgG and immunoglobulin M [IgM])
- HBV: Hepatitis B surface antigen (HbsAg), anti-Hepatitis B (HB) core, anti-HBs

- HCV: anti-HCV ELISA
- Parvovirus B19: anti-B19V (IgG and IgM)

Virus serology will be established during the screening period. The relevant confirmatory Polymerase Chain Reaction (PCR) testing may be performed from appropriate left-over samples as needed.

12.9.6 Urinalysis (Dipstick)

The urinalysis will include assessments for erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite and pH and will be performed at the central laboratory.

12.9.7 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. The pregnancy test may need to be repeated during the course of study in countries where mandated by national law.

12.9.8 VWD Mutational Analysis, Multimer Analysis and Human Leukocyte Antigen Genotyping

A cell pellet (buffy coat and erythrocytes) will be retained at the screening visit for VWD gene mutational analysis, VWF multimer analysis and HLA genotype determination if the information is not already available in the subject's medical history. Results from multimer analysis (see Section 12.9.10.1) may contribute to VWD gene mutational analysis. The genetic testing will be done, when the subject consents to the genetic testing.

12.9.9 Blood Group Analysis

The blood group needs to be determined during the screening period. If the information is not already available in the subject's medical history, it has to be determined at the local lab.

12.9.10 Additional Laboratory Testing in Case of Thromboembolic Events

rVWF (vonicog alfa) contains ULMW multimers because of a lack of exposure to endogenous VWF protease (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) during the manufacturing process. In vitro and in vivo cleavage of these ultralarge molecular fractions by ADAMTS13 and generation of characteristic satellite bands has been extensively demonstrated during nonclinical and clinical development. Nevertheless, the potential elevated risk of thrombosis and/or other thromboembolic complications due to the administration of ultra large molecular VWF multimers in subjects with normal levels of VWF cannot be completely excluded. Therefore VWF multimer analysis will not only be performed routinely at screening but in case of thromboembolic events, both VWF multimer analysis as well as ADAMTS13 activity will be determined to assess any relatedness of these occurrences with IP treatment.

12.9.10.1 VWF Multimer Analysis

The VWF multimer pattern will be assessed using low-resolution sodium dodecyl sulfate (SDS)–agarose gel electrophoresis. High-resolution SDS–agarose gel electrophoresis, with agarose concentrations >1.5%, will be used to determine the satellite band structure of VWF. These analyses will employ Western blot with luminescence video imaging.

12.9.10.2 ADAMTS13 Activity

VWF73 was identified as the 73 amino acid minimal region of the VWF A2 domain required for ADAMTS13 cleavage. The cleavage of this substrate will be detected by a commercially available ELISA-based Chromogenic assay (Technoclone Austria): Cleavage of immobilized VWF73 substrate is detected by a HRP-labeled antibody directed against the cleavage site of VWF73. The amount of bound antibody, which is the function of the ADAMTS13 cleavage is detected by a chromogenic substrate.

12.9.11 Soluble P-Selectin (sP-Selectin)

sP-selectin is a cell adhesion molecule (CAM) found in granules in endothelial cells (cells lining blood vessels) and activated platelets. Data for an association between the sP-selectin concentration, TTP and venous thromboembolism (VTE) are limited and the predictive value has not yet established. A commercial ELISA assay will be employed as an exploratory test. sP-selectin will be determined at the Screening visit and used as indicator for an increased thrombotic risk.

12.9.12 D-Dimer

D-dimer will be used as a marker for DVT and disseminated intravascular coagulation (DIC). While a negative result practically rules out thrombosis, a positive result can indicate thrombosis but does not rule out other potential etiologies, including a recent hemorrhage. Its main use, therefore, is to exclude thromboembolic disease where the probability is low. D-Dimer will be measured at the Screening visit and used as indicator for an increased thrombotic risk.

12.9.13 Additional Laboratory Testing in Case of Severe Hypersensitivity Reactions

If a subject develops a severe hypersensitivity reaction in the course of the clinical study, additional blood will be drawn for anti-VWF IgE antibody testing. The presence of anti-VWF IgE will be determined by using the ImmunoCAP®, a VWF-specific IgE blood test (Thermo Scientific). The basis of the ImmunoCAP® technology is a cellulose polymer as solid phase in a plastic capsule providing a large surface for protein binding. rVWF (vonicog alfa) as antigen is covalently coupled to the cellulose polymer.

Detection of specific anti-VWF IgE bound to the antigen will be accomplished by a secondary enzyme-labeled anti-human IgE antibody. Testing for binding anti-human VWF IgE antibodies will be done with 0.5 mL plasma. Antibody containing samples will be identified and quantified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.14 Assessment of Laboratory Values

12.9.14.1 Assessment of Abnormal Laboratory Values

For VWF and FVIII laboratory assessments no evaluation of clinical significance is necessary.

Each other laboratory value (except results to determine genetics of the underlying VWD disease and blood group) has to be assessed by the investigator and the assessment will be recorded on the eCRF. The investigator will determine for each abnormal laboratory value whether the value is considered clinically significant or not and provide the reference range including the units. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 12.1) and record the sign, symptom, or medical diagnosis on the AE CRF, is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.5), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, i.e. because it is due to a preexisting disease, due to a lab error, due to variation or due to another issue that will be specified.

Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator. Any abnormal laboratory value that is considered clinically significant by the investigator based on a local laboratory test result (reference range and the units to be provided) should be confirmed by a central laboratory test result for which the sample is drawn/collected within 24 hours of the abnormal finding by the local laboratory.

Any seroconversion result for HIV, HAV, hepatitis B virus (HBV), HCV, HEV, or B19V shall be re-tested.

12.10 [redacted]

12.10.1 [redacted]

12.10.2 [redacted]

[redacted]

13. STATISTICS

13.1 Sample Size and Power Calculations

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 cohort (OD and switch). A total of at least 5 type 3 VWD subjects will be followed for 12 months. 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).[1]

13.2 Datasets and Analysis Cohorts

13.2.1 Safety Analysis Set

The Safety Analysis Set will be composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

13.2.2 Full Analysis Dataset

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

13.2.3 Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set will be composed of subjects who are at least 70% compliant regarding the number of scheduled prophylactic infusions (as measured by the ratio of actual number of infusions to planned number of infusions). Only subjects who met all study entry criteria and who had no major protocol violations that might impact primary efficacy assessments will be included in the PP analysis set.

13.2.4 PK Full Analysis Set

The Pharmacokinetic Full Analysis Set (PKFAS) will be composed of all subjects who received the PK infusion and who provided acceptable data for PK and PD analysis. Acceptable PK/PD data will be defined in the Statistical Analysis Plan.

13.2.5 PK Per Protocol Analysis Set

The Pharmacokinetic 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 affecting the PK period of the study as defined in the detailed Statistical Analysis Plan.

13.3 Handling of Missing, Unused, and Spurious Data

13.3.1 General

Statistical techniques will not be used to identify and exclude any observations as outliers from the analyses. If data are considered spurious, e.g. for lack of biological plausibility, it will be documented to include the reason for exclusion and the analyses from which the data were excluded.

13.3.2 Other

1. Regarding missing data in PK records:
    - Body weight: If a subject's weight is missing from the PK infusion record, the subject's last recorded weight will be used to calculate the weight-adjusted dose.
    - Concentration:
        - Baseline concentration levels reported as below the limit of quantification will be considered to be 0. Missing VWF baseline concentration levels (VWF: RCo, VWF: AG or VWF: CB) for Type 3 subjects will be set to 0.
    - Time:
        - If start time of infusion is missing (but stop time is available) and actual collection time is available, then stop time of infusion will be taken for further calculation (i.e. time difference between actual end date/time of infusion and date/time blood sample drawn).
        - If actual collection date/time is missing and planned collection date/time is missing, then this PK time point will be taken out from the PK analysis (i.e. no data entry for this time point).
        - For all other scenarios, the planned collection date/time will be taken for further calculation.
2. Regarding missing data in AE records:
    - Handling of unknown causality assessment:
        - If a subject experiences an AE with a missing causality assessment, the relationship of the AE will be counted as "related."

- Handling of unknown severity grades:
  - If a subject experiences more than one AE categorized under the same preferred term, 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.

13.4 Methods of Analysis

The study success criteria are the objectives as stated in Section 7. “Treatment success” was defined as the extent of control of bleeding episodes achieved during this study.

13.4.1 Primary Outcome Measure

The primary outcome measure is ABR for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa). No formal statistical hypothesis test is planned for the analysis. The primary efficacy analysis will be based on the FAS and will be summarized by the two cohorts: on-demand and switch subjects. As a supportive analysis, the same analysis will also be carried out on the PP analysis set.

The spontaneous ABR while treated with rVWF (vonicog alfa) for each cohort will be estimated using a negative binomial regression. The prior ABR will be based on historical data collected from each enrolled subject.

The two ABRs (prior to prophylaxis treatment and while on prophylaxis) for each cohort will be compared within each subject using a generalized linear mixed-effects model (GLMM) (with a logarithmic link function, the default for the negative binomial distribution), accounting for the fixed effect of the two treatments. The follow-up time (in years) will be specified as an offset. The ratio of ABR while in the study to historical ABR will be estimated and reported together with the 95% confidence interval for each of the two cohorts.

The difference in on-study ABR relative to historical ABR will be also summarized descriptively.

13.4.2 Secondary Outcome Measures

In general, data for secondary efficacy analysis will be summarized by the two cohorts: on-demand and switch subjects and when applicable overall. Mean, standard deviation, median, range, quartiles will be calculated for continuous endpoints. Proportions, will be calculated for categorical endpoints. Confidence intervals at the two-sided 95% level will be provided when appropriate.

13.4.2.1 Additional Efficacy of Prophylaxis Treatment with rVWF

The number and proportion of on-demand subjects with ABR percent reduction success (i.e.≥ 25%) will be calculated together with a two-sided, 95% CI for the proportion.

The number and proportion of pdVWF switch subjects ABR preservation success will be reported together with the corresponding 95% two-sided CIs for the proportion.

The number and proportion of subjects with categorized spontaneous ABR (i.e. 0, 1-2, 3-5, more than 5 bleeds) will be reported descriptively.

Summary statistics for the total number of infusions, as well as average number of infusions per week will be provided. The total weight adjusted consumption of rVWF (vonicog alfa) during prophylactic treatment will be provided. If applicable, historical data on consumption of pdVWF prior to the study will be summarized as well.

The change in spontaneous ABR from the historical rate to that during the rVWF (vonicog alfa) prophylaxis period will be summarized by location of bleeding (GI, epistaxis, joint bleeding, menorrhagia, oral and other mucosa, muscle and soft tissue, etc.).

13.4.2.2 Pharmacokinetic and Pharmacodynamic Analysis

All PK and PD analyses will use the actual sampling times, not nominal times specified in the protocol, wherever possible. Actual sampling times will be defined as time from the start of infusion to the blood sample collection time. A deviation from the protocol-specified blood sample 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 results were biologically implausible will be eliminated from the analysis.

If any concentration data are considered spurious (e.g. lack of biological plausibility), the reason for exclusion from the analysis and the analysis from which the data point was excluded will be documented.

Details of calculation of PK and PD parameters and corresponding analysis will be given in the statistical analysis plan.

The following PK parameters, based on the initial PK assessment after a washout for on-demand subjects, will be listed and summarized descriptively for VWF:RCo, VWF:Ag and VWF:CB: IR, $T_{1/2}$, MRT, $AUC_{0-\infty}$, $AUC_{0-tlast}$, C_{max}, T_{max}, V_{ss}, and CL. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity, based on the initial PK assessment after a washout for on-demand subjects will be assessed using C_{max}, T_{max}, and $AUC_{0-tlast}$. These PD parameters will be listed and summarized descriptively. PK parameters at steady state ($AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$) for the partial dosing interval will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study for VWF:RCo, VWF:Ag and VWF:CB and summarized descriptively for subjects with the same dosing regimens. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity will be assessed using $AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$. These PD parameters will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study and will be summarized descriptively for subjects with the same dosing regimens.

For the on-demand subjects, the PK of VWF:RCo will be analyzed using a population PK approach to characterize the single and multiple dose pharmacokinetics, including associated variability assessed at after washout and at end of study, respectively. The population PK analysis will be performed in a stepwise manner as outlined below.

1. Exploratory graphical analysis of VWF:RCo versus time data for identification of potential outliers and to inform the pharmacometric analysis.
2. Population PK model development for rVWF (vonicog alfa):
    a. Evaluate alternative structural and stochastic models to describe the typical and individual rVWF (vonicog alfa) profiles.
    b. Investigate and characterize the potential for a time dependency in CL of rVWF (vonicog alfa).
    c. Evaluate, and if necessary refine, the candidate final model

Details of this Population PK analysis will be given in a separate Population PK analysis plan.

For the switch subjects, differences in $AUC_{0\text{-}tau;ss}$, $C_{max;ss}$, and $C_{min;ss}$ assessess shortly after reaching steady state and assessed at the end of the study will be assessed by the ratio of geometric means and corresponding two-sided 95% confidence intervals for VWF:RCo, VWF:Ag,VWF:CB, and FVIII:C. These analyses will be performed using a linear mixed effects model with PK assessment (i.e. factor of two levels relating to the PK assessment shortly after reaching steady state and the PK assessment at end of study, respectively) as a fixed effect and subject as a random effect based on log-transformed PK parameters. 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.

Descriptive statistics will be used to summarize VWF:RCo, VWF:AG and VWF:CB and FVIII:C levels for each nominal time point on the PK curve.

For all subjects in the PKFAS activity/concentration vs. time curves will be prepared.

Formulas for PK parameters IR, $T_{1/2}$, MRT, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}tlast}$, C_{max}, T_{max}, V_{ss}, and CL, $AUC_{0\text{-}tau;ss}$, $C_{max;ss}$, $T_{max;ss}$,and $C_{min;ss}$ will be given in the statistical analysis plan and will be derived using non-compartmental methods in WinNonlin. Analysis of these parameters will be carried out on the PKFAS as well as on the PKPPAS.

13.4.2.3 Safety

Safety analysis will be performed overall and by the two cohorts: on-demand and switch subjects.

TEAEs are defined as AEs with start dates on or after the first exposure to IP. Summaries of AEs will be based on TEAEs unless otherwise indicated.

Occurrence of AEs and SAEs will be summarized descriptively, by system organ class and preferred term. The number and percentage of subjects who experienced AEs and SAEs, and the number of AEs and SAEs will be tabulated. In addition, the number of subjects who experienced AEs assessed as related to IP by the investigator, and the number of IP-related AEs will be tabulated. The number of patients with AEs by severity will be presented similarly.

A listing of all AEs will be presented by subject identifier, age, sex, preferred term and 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.

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 infusion, irrespective of being related or not related to treatment. Temporally associated AEs will be presented in summary tables.

AEs that occurred before first IP infusion will be listed separately.

Adverse events of special interest (AESI), such as hypersensitivity reactions and thromboembolic events, will be monitored throughout the study and statistical analysis will be conducted based on the search criteria (eg, standardised MedDRA queries [SMQ]) determined prior to database lock, and summarized.

For immunogenicity, frequency counts and percentages will be calculated for 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. Clinically significant changes relative to baseline in vital signs and clinical laboratory parameters (hematology, clinical chemistry) will be reported.

13.4.3 Exploratory Outcome Measures

[redacted]

13.4.3.1 [redacted]

[redacted]

13.4.3.2 [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

13.4.3.3 [redacted]

[redacted]

13.4.3.4 [redacted]

[redacted]

13.5 Planned Interim Analysis of the Study

No formal interim analysis is planned for this study.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Trial Agreement (CTA). If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the CTA.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable national and local regulatory requirements as described in the CTA. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

15.1.1 Investigator Report and Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the CTA. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the CTA. Auditing processes specific to the study will be described in the audit plan.

15.5 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. Also, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing whenever pdVWF is used instead of rVWF (vonicog alfa). The reason for this use must also be provided to the sponsor.The sponsor (Baxalta) will also ensure the responsible EC and relevant competent authority are notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.6 Laboratory and Reader Standardization

A central laboratory/reader will be used for all clinical assessments except for pregnancy testing and blood group test (refer to Section 12.9). Local laboratories are requested to provide their laboratory specifications of the individual tests that are also being tested locally.

16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the CTA.

16.2 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the CTA.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

16.3 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients and/or their legally authorized representative must sign an informed consent form before entering into the study according to applicable national and local regulatory requirements and ICH GCP. Before use, the informed consent form will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 16.2). The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable national and local regulatory requirements. Patients or their legally-authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent form, patients or their legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised informed consent form, which have been approved by the applicable EC and regulatory authorities, will be provided by the investigator to the subjects who consented to participate in the study

16.4 Data Monitoring Committee

This study will be monitored by aDMC. The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. 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 stop a trial if it finds toxicities or if treatment is proven to be not beneficial. Details will be defined in the DMC charter.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the CTA.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.7), records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, CRFs, SAERs, laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

If electronic format CRFs are provided by the sponsor, only authorized study site personnel will record or change data on the CRFs. If data is not entered on the CRFs during the study visit the data will be recorded on paper and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (e.g., ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the CTA.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the CTA.

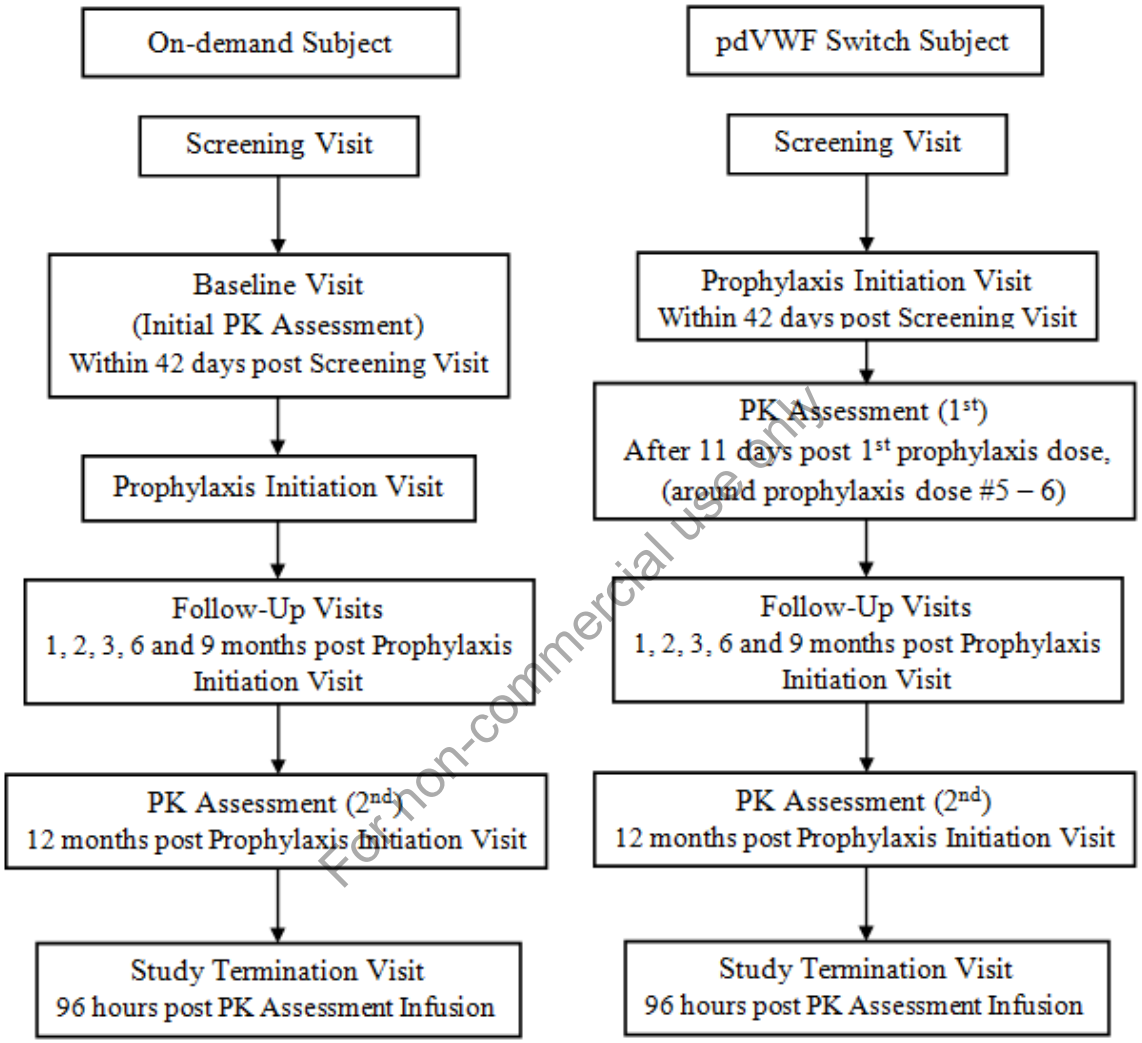
19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the CTA.

20. SUPPLEMENTS

20.1 Study Flow Chart

Figure 1
Study Design for Baxalta Clinical Study 071301



20.2 Schedule of Study Procedures and Assessments

Table 6a
Schedule of Study Procedures and Assessments for On-demand Subject

Procedures/ Assessments	Screening Visit	Baseline Visit (PK-assessment visit)			Prophylaxis Initiation Visit	Interval/Follow-Up Study Visits					PK Assessment at Study Completion			Termination Visit
		Pre-infusion[g]	Infusion	Post-infusion[g]		1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion[g]	Infusion	Post-infusion[g]	Conducted at the 96 hour postinfusion PK Assessment
											12 month ± 2 weeks			
Informed Consent [a]	X													
Eligibility Criteria	X													
Medical History[b]	X													
Concomitant Medications[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-drug Therapies[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X			X	X	X	X	X	X	X			X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Bleeding Episodes and Treatment and Hemostatic Efficacy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratories	X	X		X	X[h]	X	X	X	X	X	X		X	X
Vital Signs[d]	X	X		X	X	X	X	X	X	X	X		X	X
ECG	X								X					X
IP Treatment[e]			X		X	X	X	X	X	X		X		
IP Consumption / Treatment Compliance						X	X	X	X	X				
Subject Diary					X	X	X	X	X	X				
[redacted]	X[f]								X					X

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[a]) Occurs at enrollment (before screening).
[b]) Including documented history of on-demand treatment for the past 12 months (up to 24 months if available) and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 (up to 24) months.
[c]) Including all medications and non- drug therapies taken in the 2 weeks prior to study entry and all the concomitant medications and non-drug therapies during the course of the study.
[d]) Vital signs: height, weight, body temperature, pulse rate, respiratory rate, and blood pressure. Height is only required at the screening visit. The time points for pre- and post-infusion measurements are (weight is measured pre-infusion only): within 30 minutes before infusion start and 30 ± 15 minutes post-infusion.
[e]) IP treatment after the prophylactic treatment initiation visit at the site will be continued as home-treatment if the subject qualifies; a wash-out period of at least 72 hours is required after the last IP infusion before the follow-up visit. IP infusion will be given at the study site after the blood sample for immunology testing and IR determination is drawn.
[f]) Can be done either at the screening or the baseline visit.
[g]) Time points for PK blood draws: 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 (the 96 hr sampling can be omitted if not allowed by the dosing interval).
[h]) If a subject did not undergo PK assessment, laboratory assessments will be performed at this visit.

Table 6b
Schedule of Study Procedures and Assessments for pdVWF Switch Subject

Procedures/ Assessments	Screening Visit	Prophylaxis Initiation Visit	PK Assessment (at prophylaxis dose #5-6)			Interval/Follow-Up Study Visits					PK Assessment at Study Completion			Termination Visit
			Pre-infusion[g]	Infusion	Post-infusion[g]	1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion[g]	Infusion	Post-infusion[g]	Conducted at the 96 hour postinfusion PK Assessment
											12 month± 2 weeks			
Informed Consent [a]	X													
Eligibility Criteria	X													
Medical History[b]	X													
Concomitant Medications[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-drug Therapies[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X	X			X	X	X	X	X	X			X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Bleeding Episodes and Treatment and Hemostatic Efficacy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratories	X	X	X		X	X	X	X	X	X	X		X	X
Vital Signs[d]	X	X	X		X	X	X	X	X	X	X		X	X
ECG	X								X					X
IP Treatment[e]		X		X		X	X	X	X	X		X		
IP Consumption / Treatment Compliance						X	X	X	X	X				
Subject Diary		X				X	X	X	X	X				
[redacted]	X[f]								X					X

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Continued

[a]) Occurs at enrollment (before screening).
[b]) Including documented history of prophylaxis treatment for the past 12 months (up to 24 months if available) and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 (up to 24) months.
[c]) Including all medications and non- drug therapies taken in the 2 weeks prior to study entry and all the concomitant medications and non-drug therapies during the course of the study.
[d]) Vital signs: height, weight, body temperature, pulse rate, respiratory rate, and blood pressure. Height is only required at the screening visit. The time points for pre- and post-infusion measurements are (weight is measured pre-infusion only): within 30 minutes before infusion start and 30 ± 15 minutes post-infusion.
[e]) IP treatment after the prophylactic treatment initiation visit at the site will be continued as home-treatment if the subject qualifies; a wash-out period of at least 72 hours is required after the last IP infusion before the follow-up visit. IP infusion will be given at the study site after the blood sample for immunology testing and IR determination is drawn.
[f]) Can be done either at the screening or the prophylaxis initiation visit.
[g]) Time points for PK blood draws: 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 (the 96 hr sampling can be omitted if not allowed by the dosing interval).

20.2.1 Summary Schedule of Visit Assesments for Surgical Bleeding

Table 7
Summary Schedule of Visit Assesments for Surgical Bleeding

Procedures/ Assessments	**Surgical procedure**				**Post-Operative Day 7 Visit (± 1 day)**	**Post-Operative Day 14 Visit (± 2 day)**
	Priming Dose Procedures (12-24 hours prior to surgery)	**Loading Dose Procedures (≤ 3 hours prior to surgery)**	**Intraoperative**	**Postoperative (day 1 → end of perioperative IP treatment)[a]**		
ECG						X
Physical examination[b]	X	X		X	X	X
Adverse events	X	X	X	X	X	X
Laboratories[c]	X	X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X
IP treatment: rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) or rVWF (vonicog alfa) only infusion	X	X	X as required	X as required	X as required	X as required
Concomitant medications and non-drug therapy	X	X	X	X	X	X
[redacted]						X
Hemostatic efficacy assessments[e]			X	X	X	X
Blood loss		X estimated	X actual	X	X[f]	X[f]
Treatment days estimate		X				

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Continued

[a] The assessments will be performed daily until perioperative IP treatment end (potentially multi-visits)
[b] Physical Examination: within 2 hours prior to IP infusion start
[c] For laboratory assessments, see Table 9
[d] Vital signs: within 30 minutes before infusion start and 30 ± 15 minutes post-infusion
[e] Completed immediately postsurgery by the operating surgeon 24 hours post last IP infusion or at Day 14 visit (whichever occurs first) by the investigator
[f] In case bleeding still ongoing

20.3 Clinical Laboratory Assessments

Table 8a
Clinical Laboratory Assessments for On-demand Subject

Procedures/ Assessments	Screening Visit	Baseline Visit (PK-assessment visit)			Prophylaxis Initiation Visit[k]	Interval/Follow-Up Study Visits					PK Assessment[m] at Study Completion			Termination Visit
		Pre-infusion	Infusion	Post-infusion		1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion	Infusion	Post-infusion	Conducted at the 96 hour postinfusion PK Assessment
											12 month± 2 weeks			
Hematology [a]	X	X		X	X	X	X	X	X	X	X		X	X
Clinical Chemistry[b]	X	X		X	X	X	X	X	X	X	X		X	X
Coagulation Panel/ PK assessment[c]	X	X		X	X	X	X	X	X	X	X		X	
Immunogenicity[d]	X	X			X[l]	X	X	X	X	X	X			X
Viral Serology[e]	X													
Urinalysis[f]	X													
VWD Gene Mutational Analysis / HLA genotype analysis and Analysis of VWF multimers[g]	X													
sP-selectin and D-dimer	X[h]													
Blood Group[i]	X													
Pregnancy Test[j]	X													

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Continued

[a] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. Hematology assessments during PK assessments will be determined prior to IP infusion and 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours thereafter. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

[b] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin. Clinical chemistry will be determined prior to IP infusion and after 24 ± 2 h, 48 ± 2 hours and 72 ± 2 hours during the PK assessments. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

[c] Coagulation panel/PK assessment (also refers to IR pre/post dose assessments at prophy initiation visit and each follow-up visit): PT, INR and aPTT (only for screening), VWF:RCo, VWF:Ag, VWF:CB, FVIII:C,; during the PK assessment at the baseline visit blood samples will be drawn 30 min prior PK infusion; once the PK infusion is completed 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 and VWF:RCo, VWF:CB, VWF:Ag, FVIII:C will be determined; for follow-up visits, IR samples will be drawn within 30 minutes pre-infusion and 30 ± 5 minutes post-infusion. During screening and in case of thromboembolic event VWF multimers and ADAMTS13 will be analyzed to judge on a possibly relatedness to UHMW fractions of the IP.

[d] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII –Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG . In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined. For on-demand subjects, a washout period of at least 72 hours after the last IP infusion is required before blood samples for immunogenicity assessments can be drawn.

[e] Viral Serology 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; HIV-1/HIV-2 Antibodies

[f] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH

[g] Not required if available in the subject's medical history; VWF multimers: additionally in case of thromboembolic events

[h] At screening and in case of thromboembolic events

[i] Blood group assessment major blood group (local laboratory) only if not available in the subject's medical history

[j] Serum pregnancy test (in females of child-bearing potential if no urine sample is available)

[k] The last post-infusion laboratory assessments coincidence with the initiation visit for prophylactic treatment. After the blood samples are drawn for laboratory assessment for the 96 h post infusion PK assessment, the subject receives the first IP infusion for prophylactic treatment (prophylactic treatment initiation visit).

[l] Only needed for subjects without PK assessment prior to their first IP infusion in this study.

[m] A steady state full PK analysis will be performed at the end of the study. 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), the 96 hr sampling can be omitted if not allowed by the dosinig interval.

Table 8b
Clinical Laboratory Assessments for pdVWF Switch Subject

Procedures/ Assessments	Screening Visit	Prophylaxis Initiation Visit	PK Assessment[k] (at prophylaxis dose #5-6)			Interval/Follow-Up Study Visits					PK Assessment[k] at Study Completion			Termination Visit
			Pre-infusion	Infusion	Post-infusion	1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion	Infusion	Post-infusion	Conducted at the 96 hour postinfusion PK Assessment
											12 month± 2 weeks			
Hematology [a]	X	X	X		X	X	X	X	X	X	X		X	X
Clinical Chemistry[b]	X	X	X		X	X	X	X	X	X	X		X	X
Coagulation Panel/PK assessment[c]	X	X	X		X	X	X	X	X	X	X		X	
Immunogenicity[d]	X	X				X	X	X	X	X	X			X
Viral Serology[e]	X													
Urinalysis[f]	X													
VWD Gene Mutational Analysis / HLA genotype analysis and Analysis of VWF multimers[g]	X													
sP-selectin and D-dimer	X[h]													
Blood Group[i]	X													
Pregnancy Test[j]	X													

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Continued

[a)] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. Hematology assessments during PK assessments will be determined prior to IP infusion and 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours thereafter. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

[b)] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin. Clinical chemistry will be determined prior to IP infusion and after 24 ± 2 h, 48 ± 2 hours and 72 ± 2 hours during the PK assessments. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

[c)] Coagulation panel/PK assessment (also refers to IR pre/post dose assessments at prophy initiation visit and each follow-up visit): PT, INR and aPTT (only for screening), VWF:RCo, VWF:Ag, VWF:CB, FVIII:C,; during the PK assessment blood samples will be drawn 30 min prior PK infusion; once the PK infusion is completed 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 and VWF:RCo, VWF:CB, VWF:Ag, FVIII:C will be determined; for follow-up visits, IR samples will be drawn within 30 minutes pre-infusion and 30 ± 5 minutes post-infusion. During screening and in case of thromboembolic event VWF multimers and ADAMTS13 will be analyzed to judge on a possibly relatedness to UHMW fractions of the IP.

[d)] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII –Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG. In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined. For switch subjects, the wash out period may be reduced to the time interval between their pdVWF prophy infusions.

[e)] Viral Serology 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; HIV-1/HIV-2 Antibodies

[f)] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH

[g)] Not required if available in the subject's medical history; VWF multimers: additionally in case of thromboembolic events

[h)] At screening and in case of thromboembolic events

[i)] Blood group assessment major blood group (local laboratory) only if not available in the subject's medical history

[j)] Serum pregnancy test (in females of child-bearing potential if no urine sample is available)

[k)] A full steady state PK analysis will be performed. 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) , the 96 hr sampling can be omitted if not allowed by the dosinig interval.

20.3.1 Laboratory Sampling for Surgical Bleeding

Table 9
Laboratory Samplinga for Surgical Bleeding

Procedures/ Assessments	**Surgical procedure**				**Post-Operative Day 7 Visit (± 1 day)**	**Post-Operative Day 14 Visit (± 2 day)**
	Priming Dose Procedures (12-24 hours prior to surgery)	**Loading Dose Procedures (≤ 3 hours prior to surgery)**	**Intraoperative**	**Postoperative (day 1 → end of perioperative IP treatment)[b]**		
Hematology[c]	X (w/o Differential)	X[d] (w/o Differential)		X (w/o Differential)	X	X
Clinical Chemistry[e]	X	X[d]			X	X
Coagulation panel[f]	X	X	X	X	X	X
VWF inhibitory and binding antibodies, antibodies to other proteins[g]	X	X	X if excessive or unexplainedbleeding	X	X	X
Urinalysis[h]					X	X
VWF Multimers[i]						
Anti VWF IgE antibody testing only in case of allergic reaction/ anaphylaxis						

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Continued

[a)] Blood draws are within 3 hrs prior to infusion start, expect that for the priming dose blood draw is within 30 minutes prior to infusion start. For coagulation panel, an additional 30 ± 5 minutes post-infusion blood draw is needed.
[b)] The assessments will be performed daily until perioperative IP treatment end (potentially multi-visits)
[c)] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.
[d)] Not required if sample already drawn at the time of the priming dose
[e)] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin.
[f)] Coagulation panel: VWF:RCo, VWF:Ag, FVIII:C PT INR and aPTT; in additiona to pre-infusion, 30 ± 5 minutes post infusion blood draw is needed.
[g)] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII – Neutralizing and Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG. In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined.
[h)] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH
[i)] VWD multimers and ADAMTS13 during the study only in case of thrombotic events

20.4 Contraceptive Methods for Female Subjects of Childbearing Potential

In this study, subjects who are women of childbearing potential must agree to utilize a highly effective contraceptive measure throughout the course of the study and for 30 days after the last administration ofIP. In accordance with the Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials (version 2014-09-15)[ii], birth control methods which may be considered as highly effective include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable[iii]
- Intrauterine device (IUD)[iii]
- Intrauterine hormone-releasing system (IUS) [iii]
- Bilateral tubal occlusion[iii]
- Vasectomised partner(s)[iii]
- Sexual abstinence during the entire study period

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

[ii] Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf.

[iii] Contraception methods that are considered to have low user dependency.

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19. [redacted]

20. [redacted]

21. [redacted]

22. SUMMARY OF CHANGES

Protocol 071301: Global Amendment 6: 2018 MAR 12

Replaces: Amendment 3: 2017 AUG 03

In this section, changes from the previous version of the Protocol, dated 2017 AUG 03, are described and their rationale is given.

1. Throughout the document
   Description of Change:
   Minor grammatical and/or administrative changes and/or rewording have been made.
   Purpose for Change: To improve the readability and/or clarity of the protocol.

2. Throughout the document
   Description of Change:
   INN was added to rVWF and ADVATE by changing rVWF to rVWF (vonicog alfa) and changing ADVATE to ADVATE (rFVIII, octocog alfa).
   Purpose for Change: To add INN.

3. Section 2, Section 12.1.2
   Description of Change:
   Bleeding events that meet seriousness criteria should be reported on both SAE eCRF and SAE report form. Section 12.1.2.3 was added as a reference for SAE assessment.
   Purpose for Change: To provide further clarifications on SAE reporting.

4. Synopsis (Clinical condition(s)/indication(s)), Section 6.4, Section 13.1
   Description of Change:
   Original text:
   Subjects with severe von Willebrand disease (VWD) requiring prophylactic treatment with coagulation factor replacement.
   New text:
   Subjects with severe von Willebrand disease (VWD) **(baseline VWF:RCo <20 IU/dL)** requiring prophylactic treatment with coagulation factor replacement.
   Purpose for Change: To add definition of severe VWD.

5. Synopsis (Planned study period), Section 8.2
   Description of Change:
   The initiation/completion and duration of the study were updated per the new timeline.
   Purpose for Change: To reflect the new study timeline.

6. Synopsis (Study purpose, Study design), Section 7.1, Section 8.1
   Description of Change:
   Hypersensitivity was added for safety evaluation; PK and pharmacoecnomics evaluation was added.
   Purpose for Change: To provide further clarifications to the purpose of the study.

7. Synopsis (Primary objective), Section 7.2
   Description of Change:
   Original text:
   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 and to compare it to the subject's historical ABR **for spontaneous bleeding episodes during on-demand treatment**.
   New text:
   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 and to compare it to the subject's historical ABR for spontaneous bleeding episodes.
   Purpose for Change: To remove wording to accommodate pdVWF switch subject cohort, which is a new study cohort added in this amendment.

8. Synopsis (Secondary objectives), Section 7.3
   Description of Change:
   [redacted]. Additional wording was added to clarify the objectives.
   Purpose for Change: Remove some of the objectives ([redacted]) and add clarification.

9. Synopsis (Exploratory objectives, Exploratory outcome measures), Section 7.4, Section 8.3.3
Description of Change:
[redacted] and additional wording was added to clarify the assessments.
Purpose for Change: Clarification and adding additional objectives/assessments.

10. Synopsis (Study Design), Section 8.1
Description of Change:
Additional details about the study design were added for on-demand and the switch cohort.
Purpose for Change: To provide further clarification and to add study design for the switch cohort.

11. Synopsis (Primary outcome measure), Section 8.3.1
Description of Change:
Original text:
Prospectively recorded ABR for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF **and the subjects' historical ABR for spontaneous bleeding episodes during on-demand treatment**.
New text:
Annualized bleeding rate (ABR) for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa).
Purpose for Change: To remove the unnecessary text.

12. Synopsis (Secondary outcome measures), Section 8.3.2
Description of Change:
Rewording some of the exisiting secondary outcome measures (efficacy and safety) to provide clarification. New efficacy outcome measures were added to further access the efficacy of prophylaxis for switch subjects. Clinically significant changes in vital signs and clinical laboratory parameters were added as one additional safety measure. New steady-state PK parameters were added. PD parameters were added. [redacted].
Purpose for Change: To provide further clarifications and to add new outcome measures for switch subjects. And to remove some of the outcome measures ([redacted])

13. Synopsis (Investigational product(s), dose and mode of administration)
Description of Change:
Prophylaxis dosing guidelines were added for the pdVWF switch subjects.
Purpose for Change: To add dosing guide for the switch subjects.

14. Synopsis (Targeted accrual, sample size calculation), Section 6.4, Section 13.1
Description of Change:
Sample size was increased and targeted accrual of each cohort was added and a followup period of 12 months was added.
Purpose for Change: To update the sample to reflect the adding of switch cohort.

15. Synopsis (Inclusion criteria, Exclusion criteria), Section 9.1, Section 9.2
Description of Change:
Criteria for the switch subjects were added.
Criteria added to clarify no pre-planned surgery is allowed.
Purpose for Change: To update for the eligibility of switch subjects and to add some clarity.

16. Synopsis (Planned statistical analysis), Section 13.4
Description of Change:
Changes were made throughout the section according to the updated outcome measures. Remove the planned analysis of exploratory outcome measure from synopsis to avoid redundance
Purpose for Change: To better test the updated outcome measures.

17. Section 5
Description of Change:
New abbreviations were added.
Purpose for Change: Clarification.

18. Section 6.5, Section 6.5.2, Section 6.5.2.4, Section 6.5.2.5
Description of Change:
Summary of recently completed clinical study 071101 was added as section 6.5.2.4, the summary of 071401 was moved to section 6.5.2.5 .
Purpose for Change: To provide clinical study summary for study 071101.

19. Section 6.5.2.3
Description of Change:
To add wording about the basis of the dosing for the current study.
Purpose for Change: To provide clarification.

20. Section 6.6
Description of Change:
Original text:
He/she may benefit from a product that minimizes excessive FVIII administration.
New text:
He/she may benefit from a product that minimizes excessive FVIII administration **and thus allowing individualized dosing of VWF at optimal levels**.
Original text:
By using a recombinant product, the risk of **contamination with blood derived viruses or variant Creutzfeldt-Jakob Disease** associated with the use of products of human or animal origin has been **virtually** eliminated.
New text:
By using a recombinant product, the risk of **transmission of adventitious agents and other blood-borne pathogens** associated with the use of products of human or animal origin has been eliminated.
Purpose for Change: To provide accuracy and clarification.

21. Section 6.6
Description of Change:
Original text:
These benefits outweigh the following potential risks of rVWF.
New text:
These benefits outweigh the following **identified or** potential risks of rVWF
Purpose for Change: To provide accuracy since Thromboembolic events has been upgraded to identified risk.

22. Section 8.5
Description of Change:
Updates were made based on safety considerations.
Purpose for Change: To avoid unnecessary study stop.

23. Section 8.6.3
Description of Change:
Wording was added to clarify that partial vials are not allowed to use.
Wording about mixing of two products was removed as it is not allowed any more.
Purpose for Change: To provide clarification on IP administration.

24. Section 8.6.4.1
Description of Change:
Details about PK assessment IP treatment were added for both on-demand and switch cohorts.
Purpose for Change: To provide more details and clarifications.

25. Section 8.6.4.2
Description of Change:
Prophylaxis initiation treatment was updated to be also applicable to the switch subjects and the dosing details were removed from this section (moved to Section 8.6.4.3).
Purpose for Change: To provide details to accommodate newly added switch cohort.

26. Section 8.6.4.3, Section 8.6.4.3.1, Section 8.6.4.3.2
Description of Change:
Detailed instructions of prophylaxis dosing and dosing adjustment were added to this section for both on-demand and pdVWF switch subjects. Home treatment rules were also made applicable to switch subjects, and made correction that the investigator is responsible for the home treatment procedures.
Purpose for Change: To provide details and clarifications to accommodate newly added switch cohort.

27. Section 8.6.4.4.1, Section 10.3.1
Description of Change:
Added the requirement of documentation the reason for the use of any non-IP product or therapy.
Purpose for Change: To ensure proper documentation of non-IP product use.

28. Section 8.6.4.4.2
Description of Change:
Added the wording about dose adjustment and the optional use of ADVATE.
Purpose for Change: To provide further clarification.

29. Section 8.6.4.5
Description of Change:
Sentence was added to clarify no pre-planned surgery is allowed.
Purpose for Change: To add some clarity.

30. Section 8.6.4.5.2
Description of Change:
Added description of priming dose for surgery.
Purpose for Change: To provide further clarification.

31. Section 8.6.4.5.3
Description of Change:
Added description of loading dose for surgery.
Purpose for Change: To provide further clarification.

32. Section 8.6.4.6, Section 12.6.1
Description of Change:
Added the details about prophylaxis measures against thromboembolism.
Purpose for Change: To ensure safety monitoring of thromboembolic events.

33. Section 8.6.5
Description of Change:
Added the wording about the requirement to monitor temperature excursions at the subject's home.
Purpose for Change: To ensure IP is stored as specified in the Pharmacy Manual.

34. Section 9.4
Description of Change:
Original text:
Subjects who develop a neutralizing inhibitor to rVWF and/or ADVATE (biological assays).
New text:
Subjects who develop a neutralizing inhibitor to rVWF and/or ADVATE (biological assays) **that results in significant clinical effect, including but not limited to increasing the weekly dose of rVWF by ≥ 50%.**
Purpose for Change: To provide more clarifications.

35. Section 9.4
Description of Change:
One more discontinuation criteria was added.
Purpose for Change: To avoid the continue of non-compliance subjects.

36. Section 10.3.1
Description of Change:
Added the wording to clarify the wash-out period of the screening visit and the timing of the subsequent visit for switch subjects.
Purpose for Change: To clarify for switch subjects.

37. Section 10.3.2
Description of Change:
Wording was added to specify this visit only applicable to on-demand cohort.
Purpose for Change: To provide clarification.

38. Section 10.3.3
Description of Change:
Wording was added to specify the timing of this visit for the switch cohort.
Purpose for Change: To provide clarification.

39. Section 10.3.4
Description of Change:
The initial steady-state PK assessment that only applicable to the switch subjects was specified in this section.
Purpose for Change: To accommodate PK assessment of switch subjects.

40. Section 10.3.5, Section 10.3.6, Section 10.3.7, Section 10.3.8, Section 10.3.9
Description of Change:
The original sections from 10.3.4 – 10.3.8 became 10.3.5 – 10.3.9 due to the insertion of new section 10.3.4.
Purpose for Change: To accommodate the insertion of new Section 10.3.4.

41. Section 10.3.7
Description of Change:
The value of prophylaxis dose was removed since it was not correct for switch patients. The different wash-out period for switch subjects was specified.
Purpose for Change: To make corrections and to make clarifications for switch subjects.

42. Section 10.3.9
Description of Change:
Wording was added to clarify that the EOS PK assessment also applicabe for switch subjects and the wash-out requirement for switch subjects was added. The details about PK parameters were removed (specified in other sections).
Purpose for Change: To provide clarifications for switch subjects.

43. Section 10.4
Description of Change:
Added more clarification about the use of Antifibrinolytics.
Purpose for Change: To provide further clarifications.

44. Section 10.5
Description of Change:
Added more details about what would be recorded in the diary.
Purpose for Change: To provide further clarifications.

45. Section 11.2, Section 12.5
Description of Change:
Specified the need of location for historical bleeds records. Clarified that it is good to have upto 24 months of historical records if available.
Purpose for Change: To provide further clarifications.

46. Section 11.3
Description of Change:
Added more details about what would be needed for switch subjects as the historical factor dosing and consumption records.
Purpose for Change: To provide further clarifications.

47. Section 11.5
Description of Change:
Clarify the assessment of overall assessment of hemostatic efficacy.
Purpose for Change: To provide clarifications.

48. Section 11.6
Description of Change:
Section title was updated to add PD assessment.
PK/PD assessment details including schedule, dosing, parameters, etc.
Purpose for Change: To provide instruction/protocol for PK/PD assessment.

49. Section 12.1.1.1
Description of Change:
More details about hypersensitivity reactions were specified. SAE reporting reference was added.
Purpose for Change: To provide further clarification.

50. Section 12.1.1.2
Description of Change:
More clarifications about SUSAR were added.
Purpose for Change: To provide further clarification.

51. Section 12.1.1.3
Description of Change:
More details about criteria of serious AE were added.
Purpose for Change: To provide further clarification.

52. Section 12.1.2
Description of Change:
Some wording of clarification was added for assessment of AE.
Purpose for Change: To provide further clarification.

53. Section 12.1.2.2
Description of Change:
Original text:
Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).
New text:
Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP**, is not biologically plausible per mechanism of action of the IP,** or has a much more likely alternative etiology).
Purpose for Change: To provide more clarifications.

54. Section 12.1.2.3
Description of Change:
More details about hypersensitivity reactions were specified. SAE reporting reference was added.
Purpose for Change: To provide further clarification.

55. Section 12.7
Description of Change:
Added clarification that height is only assessed on screening visit.
Purpose for Change: To provide further clarification.

56. Section 12.9, Section 12.9.14.1
Description of Change:
"Abnormal laboratory values deemed clinically significant by the investigator are to be recorded as AEs (see Section 12.1.2)." was removed due to inaccuracy.
New Text added: "Any abnormal laboratory value that is considered clinically significant by the investigator based on a local laboratory test result (reference range and the units to be provided) should be confirmed by a central laboratory test result **for which the sample is drawn/collected** within 24 hours of the abnormal finding by the local laboratory".
Purpose for Change: To provide accuracy and further clarification.

57. Section 12.9.1
Description of Change:
Section title was updated to add PD assessment.
Text was removed, and refered to Section 11.6.
Purpose for Change: To avoid duplicated text.

58. Section 12.9.3.4
Description of Change:
Wording added to specify that only confirmed positive anti-VWF inhibitor test result will be reported and will be considered as a medically significant SAE.
Purpose for Change: To clarify.

59. Section 12.10.2
Description of Change:
[redacted]
Purpose for Change: [redacted]

60. Section 13.2.2
Description of Change:
Original text:
The Full Analysis Set (FAS) will be composed of all subjects **with available bleeding data gathered during** prophylaxis IP treatment.
New text:
The Full Analysis Set (FAS) will be composed of all subjects **who receive** prophylaxis IP treatment.
Purpose for Change: To re-define FAS.

61. Section 13.2.3
Description of Change:
Details were added on how to measure the compliance.
Purpose for Change: To add clarifications.

62. Section 13.2.4
Description of Change:
Wording added to clarify PK analysis set is also for PD analysis.
Purpose for Change: To add clarifications.

63. Section 13.4.2.2, Section 13.4.2.3
Description of Change:
[redacted]
Purpose for Change: [redacted]

64. Section 13.4.3.1, Section 13.4.3.2, Section 13.4.3.3 and Section 13.4.3.4
Description of Change:
[redacted]
Purpose for Change: [redacted]

65. Section 13.5
Description of Change:
Removed the interim analysis
Purpose for Change: No interim analysis is planned.

66. Section 15.5
Description of Change:
Additional instruction was provided to ensure the compliance by adding the text "Also, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing whenever pdVWF is used instead of rVWF. The reason for this use must also be provided to the sponsor".
Purpose for Change: To ensure compliance.

67. Section 20.1
Description of Change:
The study flow chart was updated to reflect the addition of switch cohort and to illustrate the study design for this new cohort.
Purpose for Change: To update the study design.

68. Section 20.2, Section 20.2.1
Description of Change:
Some clarifications were made to the tables and the footnotes, the original table 6 was changed to 6a and specified just for on-demand subjects, table 6b that is for switch subjects was added.
Purpose for Change: To provide schedule for the switch subjects and to provide clarifications for surgery procedure schedule.

69. Section 20.3, Section 20.3.1
Description of Change:
Some clarifications were made to the tables and the footnotes, the original table 8 was changed to 8a and specified just for on-demand subjects, table 8b that is for switch subjects was added.
Purpose for Change: To provide schedule for the switch subjects and to provide clarifications for surgery lab assessments.

INVESTIGATOR ACKNOWLEDGEMENT

RECOMBINANT VON WILLEBRAND FACTOR (rVWF)

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

CLINICAL TRIAL PHASE 3

GLOBAL AMENDMENT 6: 2018 MAR 12

Replaces: AMENDMENT 3: 2017 AUG 03

OTHER PROTOCOL ID(s)
NCT Number: NCT02973087
EudraCT Number: 2016-001478-14
IND NUMBER: 013657

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT

RECOMBINANT VON WILLEBRAND FACTOR (rVWF)

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By signing below, the investigator acknowledges that he/she has read and understands this protocol, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
[redacted], MD
[redacted]
Global Clinical Development Operations
Baxalta Innovations GmbH

CLINICAL STUDY PROTOCOL

PRODUCT: Recombinant Von Willebrand Factor (rVWF, vonicog alfa)

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 SHORT TITLE: rVWF IN PROPHYLAXIS

PROTOCOL IDENTIFIER: 071301

CLINICAL TRIAL PHASE 3

LOCAL AMENDMENT 7 (GERMANY): 2018 MAY 18

Replaces:
LOCAL AMENDMENT 4 (GERMANY): 2017 AUG 04

ALL VERSIONS:
Local (Germany) Amendment 7: 2018 MAY 18
Amendment 6: 2018 MAR 12
Local (Czech Republic) Amendment 5: 2017 AUG 08
Local (Germany) Amendment 4: 2017 AUG 04
Amendment 3: 2017 AUG 03
Amendment 2: 2016 DEC 15
Amendment 1: 2016 APR 08
Original: 2014 FEB 19

OTHER ID(s)
NCT Number: NCT02973087
EudraCT Number: 2016-001478-14
IND NUMBER: 013657

Study Sponsor(s):

Baxalta US Inc.
300 Shire Way
Lexington, MA 02421,
UNITED STATES

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna,
AUSTRIA

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted]
Global Clinical Development Operations
Baxalta Innovations GmbH

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (e.g. investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) and suspected unexpected serious adverse events (SUSARs) to the ECs.

ALL SAEs, INCLUDING SUSARs, ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT.

Bleeding events that meet seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) should be reported on the SAE eCRF and SAE Report form as an SAE.

Drug Safety contact information:

Baxalta Global Drug Safety fax number: [redacted]

OR

email: [redacted]

For definitions and information on the assessment of these events, refer to the following:

- Adverse Events (AEs), Section 12.1
- SAEs, Section 12.1.1.1
- SUSARs, Section 12.1.1.2
- Assessment of AEs, Section 12.1.2
- Safety Reporting, Section 12.1.2.3

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	Recombinant von Willebrand factor (rVWF, vonicog alpha)
Name(s) of Active Ingredient(s)	Recombinant von Willebrand factor (rVWF, vonicog alpha)
CLINICAL CONDITION(S)/INDICATION(S)	
Subjects with severe von Willebrand disease (VWD) (baseline VWF: Ristocetin cofactor activity (VWF:RCo) <20 IU/dL) requiring prophylactic treatment with coagulation factor replacement	
PROTOCOL ID	071301
PROTOCOL TITLE	A prospective, phase 3, open-label, international multicenter study on efficacy and safety of prophylaxis with rVWF in severe von Willebrand disease
Short Title	rVWF in prophylaxis
STUDY PHASE	Phase 3
PLANNED STUDY PERIOD	
Initiation	2017 OCT
Primary Completion	2019 Q4
Study Completion	2019 Q4
Duration	27 months
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
The purpose of this phase 3 study is to investigate the efficacy and safety, including immunogenicity, thrombogenicity and hypersensitivity reactions, as well as pharmacokinetics (PK), [redacted] and [redacted] of prophylactic treatment with rVWF (vonicog alfa) in adult subjects with severe VWD.	
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.	
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 FVIII activity	

Exploratory Objectives	
[redacted]	
STUDY DESIGN	
Study Type/ Classification/ Discipline	Efficacy and Safety
Control Type	No control
Study Indication Type	Prophylaxis and treatment of bleeding episodes
Intervention model	Single-group
Blinding/Masking	Open-label
Study Design	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, [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 (pdVWF switch subjects) will receive prophylactic treatment with rVWF (vonicog alfa) for a 12-month period.
Planned Duration of Subject Participation	Approximately 15 months
Primary Outcome Measure	
Efficacy • Annualized bleeding rate (ABR) for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa)	
Secondary Outcome Measures	
Additional efficacy of prophylactic treatment with rVWF (vonicog alfa) • ABR percent reduction success for OD subjects defined as at least 25% reduction of ABR for spontaneous (not related to trauma) bleeding episodes during rVWF (vonicog alfa) prophylaxis relative to the subject's own historical ABR during on-demand treatment	

- ABR preservation success for pdVWF switch subjects 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 during prophylactic treatment with pdVWF
- Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 bleeding episodes during the 12-month 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
- Spontaneous ABR 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)

Safety

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

Pharmacokinetics (PK) and Pharmacodynamics (PD)

- PK parameters after a washout for on-demand 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 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 VWF:RCo, Von Willebrand factor antigen (VWF:Ag), Von Willebrand collagen binding activity (VWF:CB).
- PD parameters after a washout for on-demand subjects: C_{max}, T_{max}, and $AUC_{0-tlast}$ as measured in FVIII activity by the 1-stage clotting assay (FVIII:C).
- PK parameters at steady state for on-demand and switch subjects: area under the concentration versus time curve from 0 to end of the partial dosing interval ($AUC_{0-tau;ss}$), 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. PK parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.
- PD parameters at steady state for on-demand and switch subjects: $AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$ as measured in FVIII actvitiy by the 1-stage clotting assay (FVIII:C). PD parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.
- Time course of FVIII clotting activity (FVIII:C) levels.

Exploratory Outcome Measures	
[redacted]	
INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**Dosage form**: powder and solvent for solution for injection **Dosage frequency**: Prophylactic Treatment Subjects transitioning from on-demand treatment will receive twice weekly infusion with rVWF (vonicog alfa) at doses of 50 ± 10 IU/kg rVWF:RCo. Dosage may be individualized within this range based on: • available historical PK data • type and severity of bleeding episodes the subject has experienced in the past • monitoring of appropriate clinical and laboratory measures

	The starting dose can, after consultation with the Sponsor, be increased up to 80 U/kg if considered necessary to assure effective prophylaxis. Subjects switching from pdVWF prophylaxis treatment: the weekly dose (IU/kg) of rVWF (vonicog alfa) for each patient will be equivalent (± 10%) to the weekly VWF dose received during prophylactic treatment with pdVWF. The weekly dose should be divided into 2 infusions, 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. A once weekly dose regimen will be allowed after switch to rVWF (vonicog alfa) if the patient has been on a once weekly dose regimen with pdVWF. Dose and dose interval may, after consultation with the sponsor, be further individualized based on: • available historical PK data • type and severity of bleeding episodes the subject has experienced in the past • monitoring of appropriate clinical and laboratory measures <u>Treatment of Bleeding Episodes:</u> Dosage must be individualized based on the subject's weight, type and severity of bleeding episode and monitoring of appropriate clinical and laboratory measures. In general, an initial dose of 40-60 IU/kg VWF:RCo with or without 30-45 IU rFVIII [ADVATE, octocog alfa]/kg is recommended (rVWF:rFVIII ratio of 1.3:1: ± 0.2). In cases of major bleeding episodes, a dose of up to 80 IU/kg VWF:RCo may be infused. Subsequent doses, if necessary, will be administered with or without ADVATE (rFVIII, octocog alfa) to maintain VWF:RCo and FVIII levels for as long as deemed necessary by the investigator. **Mode of Administration:** intravenous
SUBJECT SELECTION	
Targeted Accrual	Approximately 22 adult subjects with severe VWD will be included to have ≥8 subjects in each cohort (OD and switch). A total of at least 5 type 3 VWD subjects will be followed for 12 months.
Number of Groups/ Arms/ Cohorts	Single-group

Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding:
    a. Type 1 (VWF:RCo <20 IU/dL) or,
    b. Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2M or,
    c. Type 3 (VWF:Ag ≤3 IU/dL).
2. Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.
3. For on-demand patient group, subject currently receiving on-demand treatment for whom prophylactic treatment is recommended by the investigator.
4. For pdVWF switch patient group, subject has been receiving prophylactic treatment of pdVWF products for no less than 12 months prior to screening.
5. For on-demand patient group, subject has ≥3 documented spontaneous bleeds (not including menorrhagia) requiring VWF treatment during the past 12 months.
6. Availability of records to reliably evaluate type, frequency and treatment of bleeding episodes during at least 12 months preceding enrollment. Up to 24 months of retrospective data should be collected if available. Availability of dosing and factor consumption during 12 months (up to 24 months) of treatment prior to enrollment is required for pdVWF switch subjects and is desired (but not a requirement) for on-demand subjects.
7. Subject is ≥18 years old at the time of screening and has a body mass index ≥18 but ≤30 kg/m^2.
8. If female of childbearing potential, subject presents with a negative blood/urine pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.
9. Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

Subjects who meet ANY of the following criteria are not eligible for this study:

1. The subject has been diagnosed with Type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD (e.g., qualitative and quantitative platelet disorders or elevated prothrombin time (PT)/international normalized ratio [INR] >1.4).
2. The subject is currently receiving prophylactic treatment with more than 5 infusions per week.
3. The subject is currently receiving prophylactic treatment with a weekly dose exceeding 240 IU/kg.
4. The subject has a history or presence of a VWF inhibitor at screening.
5. The subject has a history or presence of a FVIII inhibitor with a titer ≥0.4 Bethesda units (BU) (by Nijmegen modified Bethesda assay) or ≥0.6 BU (by Bethesda assay).
6. The subject has a known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins.
7. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
8. The subject has a medical history of a thromboembolic event.

9. The subject is human immunodeficiency virus (HIV) positive with an absolute Helper T cell (CD4) count <200/mm^3.
10. The subject has been diagnosed with significant liver disease per investigator's medical assessment of the subject's current condition or medical history or as evidenced by any of the following: serum alanine aminotransferase (ALT) greater than 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).
11. The subject has been diagnosed with renal disease, with a serum creatinine (CR) level ≥2.5 mg/dL.
12. The subject has a platelet count <100,000/mL at screening.
13. The subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to signing the informed consent.
14. The subject is pregnant or lactating at the time of enrollment.
15. Patient has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
16. The subject has participated in another clinical study involving another investigational product (IP) or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
17. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
18. The subject is scheduled for a surgical intervention.
19. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
20. The subject has a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
21. The subject is in prison or compulsory detention by regulatory and/or juridical order
22. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.

Delay criteria

1. If the subject presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) the screening visit will be postponed until the subject has recovered.

STATISTICAL ANALYSIS

Sample Size Calculation

Approximately 22 adult subjects with severe VWD will be included in the study. The aim is to have ≥8 subjects in each cohort (OD and switch). A total of at least five type 3 VWD subjects will be followed for 12 months. 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).[1]

Planned Statistical Analysis

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

The Safety Analysis Set will be composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

The Per-Protocol (PP) Analysis Set will be composed of subjects who are at least 70% compliant regarding the number of scheduled prophylactic infusions. Only subjects who meet all study entry criteria and who have no major protocol violations that might impact primary efficacy assessments will be included in the PP analysis set.

The Pharmacokinetic Full Analysis Set (PKFAS) will be composed of all subjects who received the PK infusion and who provided acceptable data for PK and PD analysis. Acceptable PK/PD data will be defined in the Statistical Analysis Plan.

Primary Outcome Measure:

No formal statistical hypothesis test is planned for the analysis. Spontaneous ABR while treated with rVWF (vonicog alfa) for each cohort, on demand and switch subjects, will be estimated using a negative binomial regression. The prior ABR for each cohort will be based on historical data collected from each enrolled subject. The two ABRs (observed on the study and historical) will be assessed 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 ABR ratio together with a two-sided, 95% confidence interval (CI) will be reported for each cohort.

The difference in on-study ABR relative to historical ABR will be summarized descriptively.

The primary efficacy analysis will be based on the FAS and will be summarized by the two cohorts: on-demand and switch subjects. As a supportive analysis, the same analysis will also be carried out on the PP analysis set.

Secondary Outcome Measures:

In general, data for secondary efficacy analysis will be summarized by the two cohorts: on-demand and switch subjects and when applicable overall. Mean, standard deviation, median, range, quartiles will be calculated for continuous endpoints. Proportions will be calculated for categorical endpoints. Confidence intervals at the 95% level will be provided when appropriate.

Additional efficacy of prophylactic treatment with rVWF (vonicog alfa):

The number and proportion of on-demand subjects with ABR percent reduction success (i.e. $\geq 25\%$) will be calculated together with a two-sided 95% CI for the proportion.

The number and proportion of pdVWF switch subjects with ABR preservation success will be reported together with the corresponding 95% two-sided CIs for the proportion.

The number and proportion of subjects with categorized spontaneous ABR (i.e. 0, 1-2, 3-5, more than 5 bleeds) will be reported descriptively.

Summary statistics for the total number of infusions, as well as average number of infusions per week will be provided. The total weight adjusted consumption of rVWF (vonicog alfa) during prophylactic treatment will be provided. If applicable, historical data on consumption of pdVWF prior to the study will be summarized as well.

The change in spontaneous ABR from the historical rate to that during the rVWF (vonicog alfa) prophylaxis period will be summarized by location of bleeding (GI, epistaxis, joint bleeding, menorrhagia, oral and other mucosa, muscle and soft tissue, etc.).

Pharmacokinetics (PK) and Pharmacodynamics (PD):

The following PK parameters, based on the initial PK assessment after a washout for on-demand subjects, will be listed and summarized descriptively for VWF:RCo, VWF:Ag and VWF:CB: IR, $T_{1/2}$, MRT, $AUC_{0-\infty}$, $AUC_{0-tlast}$, C_{max}, T_{max}, V_{ss}, and CL. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity (FVIII:C), based on the initial PK assessment after a washout for on-demand subjects will be assessed using C_{max}, T_{max}, and $AUC_{0-tlast}$. These PD parameters will be listed and summarized descriptively.

PK parameters at steady state ($AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$) for the partial dosing interval will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study for VWF:RCo, VWF:Ag and VWF:CB and summarized descriptively for subjects with the same dosing regimens. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity (FVIII:C) will be assessed using $AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$. These PD parameters will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study and will be summarized descriptively for subjects with the same dosing regimens.

For the on-demand subjects, the PK of VWF:RCo will be analyzed using a population PK approach to characterize the single and multiple dose pharmacokinetics, including associated variability, of VWF:RCo in the study population.

For the switch subjects, differences in $AUC_{0-tau;ss}$, $C_{max;ss}$, and $C_{min;ss}$ assessess shortly after reaching steady state and assessed at the end of the study will be assessed by ratio of geometric means and corresponding two-sided 95% confidence intervals for VWF:RCo, VWF:Ag, VWF:CB, and FVIII:C. 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.

Descriptive statistics will be used to summarize VWF:RCo, VWF:Ag, VWF:CB, and FVIII:C levels for each nominal time point on the PK curve. For all subjects activity/concentration vs. time curves will be prepared.

Safety:

Safety analysis will be performed overall and by the two cohorts: on-demand and switch subjects.

Treatment-emergent AEs (TEAEs) are defined as AEs with start dates on or after the first exposure to IP. Summaries of AEs will be based on TEAEs unless otherwise indicated.

Occurrence of AEs and serious AEs (SAEs) will be summarized descriptively, by system organ class and preferred term. The number and percentage of subjects who experienced AEs and SAEs, and the number of AEs and SAEs will be tabulated. In addition, the number of subjects who experienced AEs assessed as related to IP by the investigator, and the number of IP-related AEs will be tabulated. The number of patients with AEs by severity will be presented similarly.

A listing of all AEs will be presented by subject identifier, age, sex, preferred term and 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.

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 infusion, irrespective of being related or not related to treatment. Temporally associated AEs will be presented in summary tables.

Adverse events of special interest (AESI), such as hypersensitivity reactions and thromboembolic events, will be monitored throughout the study and statistical analysis will be conducted based on the search criteria (eg, standardized MedDRA queries [SMQ]) determined prior to database lock, and summarized.

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.

Clinically significant changes relative to baseline in vital signs and clinical laboratory parameters (hematology, clinical chemistry) will be reported.

4. TABLE OF CONTENTS

Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABR	Annualized bleeding rate
ADAMTS13	A Disintegrin And Metalloproteinase with a Thrombospondin type 1 motif, number 13
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the plasma concentration /time curve from time 0 to infinity
$AUC_{0-tau;ss}$	Area under the plasma concentration /time curve from time 0 to end of the partial dosing interval
$AUC_{0-tlast}$	Area under the plasma concentration /time curve from 0 to the last measurable concentration
aPTT	Activated partial thromboplastin time
B19V	Parvovirus B19
BP	Blood pressure
BU	Bethesda Unit
BUN	Blood urea nitrogen
BW	Body weight
CAM	Cell adhesion molecule
CBC	Complete blood count
CD4	Helper T cell
CHO	Chinese hamster ovary
CI	Confidence interval
Cl	Chloride
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max;ss}$	Maximum plasma concentration during the partial dosing interval at steady state
$C_{min;ss}$	Minimum plasma concentration during the partial dosing interval at steady state
CR	Creatinine
CTA	Clinical Trial Agreement
eCRF	Electronic case report form
DMC	Data monitoring committee
DIC	Disseminated intravascular coagulation

Abbreviation	Definition
DVT	Deep vein thrombosis
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
[redacted]	[redacted]
FAS	Full analysis set
FVIII	Factor VIII
FVIII:C	Factor VIII clotting activity
GCP	Good Clinical Practice
GI	Gastrointestinal
Glu	Glucose
HAMA	Human anti- mouse antibodies
HAV	Hepatitis A virus
HB	Hepatitis B
HBs	Hepatitis B surface
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
[redacted]	[redacted]
HRP	Horseradish peroxidase
IB	Investigator's brochure
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
INR	International normalized ratio
IP	Investigational product
IR	Incremental recovery
i.v.	Intravenous

Abbreviation	Definition
K	Potassium
k.o.	Knock out
LDH	Lactate Dehydrogenase
Na	Sodium
NMC	Non-medical complaint
NOAEL	No observed adverse effect level
MRI	Magnetic resonance imaging
MRT	Mean residence time
pdVWF	Plasma derived VWF product
pdVWF/FVIII	Plasma derived VWF product containing fractions of FVIII
PBAC	Pictorial Blood Assessment Chart
PCR	Polymerase Chain Reaction
PEF	Peak expiratory flow
PK	Pharmacokinetic
PKFAS	Pharmacokinetic Full Analysis Set
PKPPAS	Pharmacokinetic Per Protocol Analysis Set
PP	Per protocol
PT	Prothrombin time
Q1, Q3	Quartile
rFVIII	Recombinant factor VIII
rVWF	Recombinant von Willebrand factor
RBC	Red blood cell count
SAE	Serious adverse event
SAER	Serious adverse event report
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
[redacted]	[redacted]
SIC	Subject identification code
SMQ	Standardised MedDRA queries
sP-selectin	Soluble P-selectin
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Terminal phase half life
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack

Abbreviation	Definition
T_{max}	Minimum time to reach the maximum concentration
$T_{max;ss}$	Minimum time to reach the maximum concentration at steady state
TTP	Thrombotic thrombocytopenic purpura
ULMW	Ultra-large molecular weight
ULN	Upper limit of normal
V_{ss}	Volume of distribution at steady state
[redacted]	[redacted]
VTE	Venous thromboembolism
VWD	von Willebrand disease
VWF	Von Willebrand factor
VWF:Ag	Von Willebrand factor antigen
VWF:CB	Von Willebrand Factor collagen binding
VWF:RCo	Von Willebrand factor: Ristocetin cofactor activity
WBC	White blood cell

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

Baxalta US Inc. (hereafter referred to as Baxalta or sponsor) has developed a human recombinant von Willebrand Factor (rVWF, vonicog alfa), which is co-expressed with recombinant factor VIII (rFVIII) in a Chinese hamster ovary (CHO) cell line and separated during the subsequent downstream process. To address concerns regarding the risk of transmission of blood-borne pathogens that may be introduced by human plasma, no exogenously added raw materials of human or animal origin are employed in the cell culture, purification, or formulation of the final container product. The only proteins present in the final container product other than rVWF (vonicog alfa) are trace quantities of murine immunoglobulin (IgG, from the immunoaffinity purification), host cell (i.e., CHO) protein, rFurin (used to further process rVWF). rVWF (vonicog alfa) is intended for the treatment of von Willebrand disease (VWD).

rVWF (vonicog alfa) has been developed under the Baxalta internal code BAX111 and is used as investigational product (IP) in this study. rVWF (vonicog alfa) may be used with or without ADVATE (rFVIII, octocog alfa) for the treatment of bleeding episodes (see Section 8.6.4.4). See Section 8.6 for further information on the IPs and their usage in this study. A detailed description of rVWF (vonicog alfa) is also provided in the Investigator's Brochure (IB).

rVWF (vonicog alfa) was granted licensure in the United States in December 2015 under the brand name VONVENDI for the on-demand treatment and control of bleeding episodes in adults diagnosed with VWD; as of the date of this protocol VONVENDI is not yet available on the market.

6.2 Clinical Condition/Indication

Von Willebrand Factor (VWF) is a large multimeric glycoprotein with a molecular weight that varies from 500 to 20,000 kDa. VWF is normally found in plasma and produced in the alpha-granules of platelets and in endothelial cell organelles known as the Weibel-Palade bodies. VWF mediates platelet adhesion and aggregation at sites of vascular injury, one of the key functions in primary hemostasis. VWF also serves to stabilize coagulation factor VIII (FVIII), where FVIII is an essential cofactor of secondary hemostasis, which leads to fibrin clot formation.[2] Qualitative and/or quantitative deficiencies of VWF lead to a highly variable bleeding diathesis known as VWD, the most common of the hereditary coagulation factor deficiencies. Penetrance of VWD is highly variable, with only a small fraction of mildly affected patients displaying clinical symptoms or a family history of a bleeding diathesis.

The current biochemical-based classification distinguishes disorders arising from partial quantitative (type 1), qualitative (type 2), or virtually complete (type 3) deficiencies of VWF. Up to 70% of VWD patients are diagnosed with type 1 VWD, which may also be associated with minor functional defects in the molecule. In general, patients with type 1 VWD display mild clinical symptoms. Approximately 20 to 30% of VWD patients are diagnosed with type 2 VWD. Type 2 VWD is further divided into 4 subtypes (A, B, N, and M), reflecting distinct classes of functional abnormalities. These defects result in abnormal functional and/or multimeric distribution patterns that facilitate their diagnosis. The bleeding diathesis is usually moderate and primarily affects the mucosal tissues. Type 2N VWD patients are sometimes misdiagnosed as mild hemophilia A. Finally, approximately 1% percent of VWD patients exhibit a total or near total absence of VWF, which is classified as type 3 VWD. The incidence of type 3 VWD is estimated at 0.5-1.0 x 10^6. This type is also associated with a very low FVIII level (typically <5%) because the VWF carrier function for FVIII is lost. Replacement of VWF alone stabilizes endogenous FVIII, resulting in hemostatic levels within several hours post-infusion. Published results from studies of a plasma-derived VWF (pdVWF) concentrate demonstrated an increase of FVIII at an approximate rate of 5.8 ± 1 IU dL^{-1} h^{-1}.[3] Type 3 VWD patients display severe hemorrhagic symptoms with bleeding predominantly in mucosal tissues, muscle and joints. All VWD patients, particularly those with type 2 or type 3 VWD, are at an increased risk for life-threatening bleeding episodes.

6.3 The Role of Prophylaxis in the Management of VWD

The goals of long term prophylaxis in VWD are to maintain VWF and FVIII at sufficient levels to reduce the frequency and duration of bleeding episodes, the need for red blood cell transfusions, and the risk of complications, such as arthropathy.[4] In contrast to hemophilia, routine prophylaxis is not as established in VWD, although prophylaxis for patients with severe VWD was in use in Sweden already during the 1950s.[5] In those early days of VWD treatment, plasma FVIII concentrates containing VWF fractions were applied for replacement therapy, which then were followed by plasma derived VWF products containing fractions of FVIII (pdVWF/FVIII).

A Swedish cohort including 37 patients with type 3 VWD under prophylactic median treatment of 11 years (range 2 to 45 years) was retrospectively analyzed.[6,7] The doses used for prophylaxis, given once weekly for at least 45 weeks per year, were calculated based on 12 to 50 IU/kg body weight (BW) of FVIII clotting activity (FVIII:C) which approximately corresponded to 24-100 IU/kg von Willebrand factor: Ristocetin cofactor activity (VWF:RCo) considering that mainly Haemate with a known VWF:RCo/FVIII:C ratio of about 2 was used. An escalation of doses from 1 to 3 dose levels was allowed depending on the frequency and severity of bleeding episodes.

The results demonstrate that under long-term prophylaxis the number of bleeds could be reduced dramatically. Whereas the median value for bleeds per year was about 10 before prophylaxis this value could be reduced to less than 1 bleed per year during prophylaxis.

The benefit of prophylaxis for such indications was retrospectively also demonstrated in a cohort of Italian patients including type 3, 2A, 2M and type 1 patients. Prophylaxis was started after severe gastrointestinal or joint bleeding episodes and completely prevented bleeding episodes in 8 of these 11 patients and largely reduced the need of blood transfusions in the remaining 3. A regimen of 40 IU rVWF:RCo/kg was applied every other day or twice a week. A prospective study on prophylaxis, the PRO.WILL study, has been initiated in Italy.[8]

The results of a prospective study investigating the prophylaxis in children and young adults showed a significantly reduced bleeding frequency and bleeding score (3 vs. 0.07; 3 vs. 0. $p<0.001$) compared to the pre-prophylaxis values. The median dose was 40 (20-47) IU/kg VWF:RCo administered mainly twice weekly in 23 patients, 3 times a week in 7 patients and 4 times a week in 2 children.[9]

The VWD Prophylaxis Network initiated the VWD International Prophylaxis (VIP) trial to investigate the role of prophylaxis in patients with severe VWD including Type 1, 2, and 3. The dose of the factor replacement product was 50 IU /kgVWF:RCo. The frequency of the dose depended on the type of bleeding and could be increased from once weekly to twice weekly or 3 times per week. For the treatment of menorrhagia the dose of 50 IU/kg VWF:RCo was given on the first day of menses for 2 cycles. The frequency could be increased to Day 1 and 2 for 2 cycles or to Day 1, 2, and 3 of menses.

The study contains both retrospective and prospective study components. Results from the retrospective study component were published, including 61 subjects on prophylactic regimen in the past 6 months prior to enrollment or subjects with a history of prophylaxis over at least 6 month.[10] Differences in annualized bleeding rates (ABR) within individuals (during prophylaxis – before prophylaxis) were significant for those with primary indications of epistaxis ($P = 0.0005$), joint bleeding ($P = 0.002$) and GI bleeding ($P = 0.001$). The difference in the group whose primary indication for treatment was abnormally heavy bleeding at menstruation ($n = 4$) was not significant ($P = 0.25$). The reduction of mucosal bleeding likely not only dependents on normal circulating levels of active VWF, but also on the presence of discrete concentrations of normal VWF inside the platelets and within endothelial matrices. The low subject number (n=4) and the treatment scheme for menorrhagia on Days 1, 2, and 3 of menses which might represent rather on-demand than prophylactic treatment may also account for the outcome in this study.

Results from the prospective study component were reported recently.[11] Eleven subjects completed the study. Six subjects had type 2A, and 5 subjects had type 3 VWD. Six subjects presented with epistaxis, 3 with GI bleeding, and 2 with joint bleeding. Seven subjects had dose escalation above the first level. Among the 10 subjects with evaluable bleeding log data, the use of prophylaxis decreased the median ABR from 25 to 6.1 (95% confidence interval [CI] of the rate difference: -51.6 to -1.7), and the median ABR was even lower (4.0; 95% CI: -57.5 to -5.3) when the subjects reached their final dosing level. The authors concluded that this was the first prospective study to demonstrate that prophylaxis with VWF concentrates is highly effective in reducing mucosal and joint bleeding rates in clinically severe VWD.

The results of the VIP study and previous investigations suggest that VWD patients with recurrent bleeding episodes and severe menorrhagia will benefit from a prophylactic VWF replacement therapy. There is evidence that up to 40% of patients with type 3 VWD experience joint bleeding which can lead to hemophilic arthropathy. Other potential indications for prophylaxis include patients with type 2A or 2B VWD with recurrent gastrointestinal bleeding, menorrhagia or frequent epistaxis.[4] Long-term prophylaxis for most patients with type 3 VWD and in some patients with type 1 or 2 VWD, depending on the pattern of bleeding, may be the treatment option of choice. Although the main experience with long-term prophylaxis is with secondary prophylaxis, primary prophylaxis starting at young age is recommended to prevent arthropathy in patients with severe VWD.[12]

However, further studies are needed to develop evidence-based guidelines for prophylactic treatment in VWD.

6.4 Populations to be Studied

A total of approximately 22 eligible, adult subjects with severe VWD (baseline VWF:RCo <20 IU/dL) are planned to be enrolled. Two cohorts of patients will be included: patients currently receiving on-demand VWF treatment (OD subjects) and patients currently on prophylactic treatment with pdVWF (pdVWF switch subjects), and the aim is to have ≥8 subjects in each of the 2 cohorts, with a total of at least 5 type 3 VWD subjects followed for 12 months. Enrolled subjects (i.e., subjects who have signed the informed consent form) will be eligible to participate in the study if they meet all of the inclusion criteria (see Section 9.1) and none of the exclusion criteria (see Section 9.2).

6.5 Findings from Nonclinical and Clinical Studies

The following summarizes the key findings from relevant nonclinical studies as well as from the completed clinical studies **070701** (Phase 1 pharmacokinetics [PK] and safety in VWD), **071001** (Phase 3 safety and efficacy in the treatment of bleeding episodes in VWD), **071101** (Phase 3 efficacy and safety in VWD subjects undergo elective surgical procedures), **071104** (Phase 1 safety and PK in hemophilia A), and **071401** (Phase 3, expanded access in a single subject with VWD). Potential risks and efficacy of rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) are summarized in the following sections. For additional information on nonclinical and clinical Phase 1 results refer to the rVWF (vonicog alfa) IB.

6.5.1 Findings from Nonclinical Studies

6.5.1.1 Primary Pharmacodynamics

Efficacy of rVWF (vonicog alfa) combined with ADVATE (rFVIII, octocog alfa) was shown in VWD animal models, which have also low endogenous FVIII levels. Time to occlusion and stable thrombus formation was assessed in the carotid occlusion model in VWD mice. The results demonstrated that rVWF (vonicog alfa) in combination with ADVATE (rFVIII, octocog alfa) acted efficiently in a dose-dependent manner and had higher efficacy than rVWF (vonicog alfa) alone or plasma derived (pd)VWF. These results were confirmed in an additional study assessing blood loss and survival in a tail tip bleeding model in VWD mice. In a VWD dog, rVWF (vonicog alfa) stabilized canine FVIII in the circulation and significantly reduced the bleeding time.

6.5.1.2 Safety Pharmacology

The anaphylactoid and thrombogenic potential of the co-infusion of ADVATE (rFVIII, octocog alfa) and rVWF (vonicog alfa) and the co-infused product's effects on blood pressure, cardiac and respiratory function and parameters of coagulation activation were investigated in 4 in vivo studies in different animal models. Safety pharmacology studies in rats, guinea pigs, rabbits, and dogs revealed no risks for anaphylactoid and thrombogenic potential of ADVATE (rFVIII, octocog alfa) in combination with rVWF (vonicog alfa). All observations in safety pharmacology studies are considered to lie within the biological variability of animal models or occurred due to known species-specific anaphylactoid effects of excipients.

6.5.1.3 Pharmacokinetics

Pharmacokinetic studies of both rVWF (vonicog alfa) alone and combined with human rFVIII (rVWF+ADVATE) were conducted in VWD mice, VWD dogs, VWD pigs, rats, and cynomolgus monkeys. Human rVWF (vonicog alfa) stabilized the endogenous FVIII in VWD mice, VWD pigs, and VWD dogs. Furthermore, the hypotheses that the area under the curve (AUC) with rVWF alone and rVWF+ADVATE is not inferior to the AUC with pdVWF (Haemate P) was tested and confirmed statistically in normal rats. The PK characteristics of ADVATE (rFVIII, octocog alfa) were not affected by co-administration of rVWF (vonicog alfa) in cynomolgus monkeys. The PK data in the FVIII knock out (k.o.) mice model are inconclusive and might not be relevant for the clinical situation. However, a stabilizing effect of VWF on FVIII could be shown in a double k.o. model in a dose dependent manner.

6.5.1.4 Toxicology

Single dose toxicity studies were conducted in C57BL/6J-mice, VWD mice, rats, rabbits, and cynomolgus monkeys. Rats, rabbits, and cynomolgus monkeys showed no signs of toxicity. Signs of microthrombosis, an exaggerated pharmacological effect, were observed in mice. Mice are not capable of sufficiently cleaving the rVWF (vonicog alfa) subunit as murine disintegrin and metalloproteinase with a thrombospondin type 1 motif, number 13 (ADAMTS13) does not decrease the ultra-large molecular weight multimers of rVWF (vonicog alfa).[13] The observed symptoms of microthrombosis are interpreted as a species-specific exaggerated pharmacological effect. Studies evaluating the safety of repeated administration of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) (daily over 14 days) were performed in a rodent (rat) and non-rodent (cynomolgus monkey) species. Reversible signs of exaggerated pharmacological effects (regenerative anemia, thrombocytopenia, and treatment-related histopathologic changes in the heart, liver, and spleen) were observed in rats that were administered 1400 U VWF:RCo/kg /day + 1080 IU ADVATE/kg/day intravenously once daily for 14 days. Also, these findings are interpreted as a species-specific exaggerated pharmacological effect due to the low susceptibility of human rVWF (vonicog alfa) to cleavage by rodent ADAMTS13.[13] No toxicologically relevant changes were evident for clinical observations, body weight, feed consumption, ophthalmology, urinalysis, coagulation, and serum chemistry parameters, platelet aggregation, and gross pathology. rVWF (vonicog alfa) combined with ADVATE (rFVIII, octocog alfa) was well tolerated in cynomolgus monkeys after daily intravenous (i.v.) (bolus) administration of 100 U VWF:RCo/kg rVWF (vonicog alfa) combined with 77 IU/kg ADVATE (rFVIII, octocog alfa) over a period of 14 days. No adverse effects could be detected in this species.

There were no signs of hemolysis, thrombosis, or thrombocytopenia after repeated intravenous application of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa). Therefore, 100 U VWF:RCo/kg/day rVWF (vonicog alfa) with or without 77 IU/kg ADVATE (rFVIII, octocog alfa) was considered the no observed adverse effect level (NOAEL) in this study, which was the highest dose tested. Anti-drug antibodies, however, were formed in both species and resulted in a significant reduction in drug exposure after 14 applications as compared to a single application. These antibodies substantially reduced the systemic exposure to the test substance as compared to a single dose administration. No adverse effects due to antibody formation were observed in both species.

rVWF (vonicog alfa) combined with ADVATE (rFVIII, octocog alfa) was well tolerated locally and no genotoxic potential was evident after 2 in vitro and 1 in vivo genotoxicity study. A study on the influence of co-administration of VWF and ADVATE (rFVIII, octocog alfa) on the immunogenicity of ADVATE (rFVIII, octocog alfa) in 3 different hemophilic mouse models (E17 hemophilic Balb/c mice, E17 hemophilic C57BL/6J mice, and E17 hemophilic human F8 transgenic mice) showed that rVWF (vonicog alfa) does not negatively impact the immunogenicity of ADVATE (rFVIII, octocog alfa) in any of the three different hemophilic mouse models.

6.5.2 Findings from Clinical Studies

Details on study design, populations enrolled, and safety and efficacy outcomes of the phase 1 studies are presented in Section 6.5.2.1 and Section 6.5.2.2, the phase 3 study in Section 6.5.2.3, and the phase 3 surgery study in Section 6.5.2.4. Information on a single subject with VWD in Study **071401** is presented in Section 6.5.2.5.

6.5.2.1 Study 070701

Phase 1 clinical study **070701** was a multicenter, controlled, randomized, single-blind, prospective 3-step, dose escalation study to investigate safety, tolerability, and PK of rVWF (vonicog alfa) combined at a fixed ratio with ADVATE (VWF:RCo/FVIII:C of 1.3 ± 0.2:1) in adults with severe VWD.[14] Subjects were enrolled in sequential cohorts in a dose escalating manner: Cohort 1, 2, and 3 received a single intravenous infusion of rVWF:ADVATE at the following doses: 2 IU/kg VWF:RCo (Cohort 1), 7.5 IU/kg VWF:RCo (Cohort 2), and 20 IU/kg VWF:RCo (Cohort 3). Subjects in Cohort 4 received a single intravenous infusion of rVWF:ADVATE and pdVWF/ADVATE at 50 IU/kg VWF:RCo in random order.

The primary endpoint was the tolerability and safety after single dose injections of rVWF:ADVATE at 2, 7.5, 20, and 50 IU/kg VWF:RCo for up to 30 days after the last IP infusion. The data generated in this phase 1 study suggest that rVWF:ADVATE up to the highest investigated dose of 50 IU/kg VWF:RCo is well tolerated and safe in adults with severe VWD. No thrombogenic risk or thrombotic thrombocytopenic purpura (TTP)-like syndrome was observed, and no neutralizing antibodies to VWF or FVIII were identified. There were no deaths or other serious adverse reactions, and no infusions were interrupted or stopped due to an AE. Overall, the reported AE profile was similar between the recombinant and plasma-derived concentrates.

Secondary endpoints were the PK assessment of VWF:RCo, von Willebrand factor antigen (VWF:Ag) and multimeric composition of rVWF (vonicog alfa) as well as FVIII:C at standardized time points after single injections of rVWF:ADVATE and pdVWF:FVIII.

The median VWF:RCo terminal half-life ($T_{1/2}$) of rVWF (vonicog alfa) at the 50 IU/kg dose was 16 hours. $T_{1/2}$ with pdVWF:FVIII at the same dose level appeared shorter at 12.58 hours, however, the limits of the 90% CI were similar (11.73 to 17.7 hours vs. 11.87 to 18.03 hours). The median $T_{1/2}$ of VWF:RCo were shorter with the lower investigated doses: 7.13 hours and 13.23 hours with the 7.5 IU/kg and 20 IU/kg doses, although these data were derived from a much smaller number of subjects.

In consequence of the missing ADAMTS13 cleavage, ultra-large molecular weight (ULMW) multimers are contained in the rVWF (vonicog alfa) final product. The immediate cleavage of these ultra-large multimers by ADAMTS13 upon release into the circulation could be demonstrated applying sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE)/Immunoblot with polyclonal anti-VWF antibodies to detect the resulting rVWF (vonicog alfa) subunit cleavage fragments.

Overall the data generated in this phase 1 study suggest that rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) is well tolerated and safe in adults with severe VWD.

6.5.2.2 Study 071104

This study was a prospective, uncontrolled, non-randomized, multicenter proof of concept study to assess safety and PK of the addition of rVWF (vonicog alfa) to ADVATE (rFVIII, octocog alfa) treatment in 12 evaluable subjects with severe hemophilia A. All subjects underwent 3 PK analyses: the first after infusion with ADVATE (rFVIII, octocog alfa) alone, the second after infusion with ADVATE (rFVIII, octocog alfa) plus 10 IU/kg rVWF (vonicog alfa) and the third after infusion with ADVATE (rFVIII, octocog alfa) plus 50 IU/kg rVWF (vonicog alfa).

The PK analysis was performed at intervals of approximately 8 to 14 days. Before each infusion for PK assessment, there was a wash-out period of at least 5 days and the subjects were not actively bleeding.

Primary outcome measures indicate that co-administration of rVWF (vonicog alfa) slightly sustain ADVATE activity with the highest observed ADVATE (rFVIII, octocog alfa) half-life of 13.74 h (CI 11.44 to 16.52) after co-infusion of 50 IU/kg ADVATE plus 50 IU/kg rVWF:RCo.

The highest improvement in ADVATE (rFVIII, octocog alfa) circulating half-life was observed in subjects with VWF:Ag levels below 100% which indicates an association between baseline VWF:Ag levels and ADVATE (rFVIII, octocog alfa) half-life increase.

No treatment related AEs or SAEs were reported. No subject withdrew due to an AE and there were no deaths. No binding antibodies to VWF, CHO, and rFurin were detectable in the confirmatory assay and no signs of a hypersensitivity to rVWF (vonicog alfa) or ADVATE (rFVIII, octocog alfa) antigen were observed. Laboratory values over time did not indicate any potential safety risk for hemophilia A patients treated with rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) in combination.

In summary, the data indicate that rVWF (vonicog alfa) co-administered with ADVATE (rFVIII, octocog alfa) up to the highest dose of 50 IU/kg VWF:RCo is well tolerated and safe in hemophilia A patients.

6.5.2.3 Study 071001

This was a phase 3, multicenter, open-label, part-randomized clinical study to assess the PK, safety, and efficacy of rVWF:rFVIII and rVWF in the treatment of bleeding episodes in adult subjects with severe type 3 and severe non-type 3 VWD.[15] A total of 49 subjects were enrolled (signed informed consent) and screened, 18 subjects were randomized (randomization only applies to Arm 1[PK50 with treatment of BE] and Arm 2 [PK50 only] see below), 37 subjects were treated with IP (all study arms), and 30 subjects completed the study.

The study consisted of 2 parts (Part A and Part B). Part A consisted of PK assessments alone (Arm 2: PK50 only [without treatment of bleeding episodes]), or PK assessments (Arm 1: PK50 and Arm 3: PK80) plus on-demand treatment period(s) of 6 months for bleeding episodes, or on-demand treatment for bleeding episodes only (Arm 4). Except for subjects in arm 2 who completed study after second PK assessment, subjects receiving treatment for PK assessments and/or bleeding episodes in Part A were to be entered into Part B to continue on-demand treatment for bleeding episodes for 6 additional months for a total of 12 months in the study.

The primary outcome measure was the number of subjects with "treatment success" (extent of control of bleeding episodes), which was defined as a mean efficacy rating score of <2.5 for a subject's IP-treated bleeding episodes during the study. The rate of subjects with treatment success was 100% (Clopper-Pearson exact 90% CI: 84.7 to 100.0) for bleeds where the assessments were made prospectively and excluding GI bleeds. Sensitivity analyses confirmed the results of the primary analysis.

Crossover results at 50 IU/kg VWF:RCo showed that the PK profile for rVWF (vonicog alfa) VWF:RCo was independent of administration alone or with rFVIII (ADVATE, octocog alpha) ($T_{1/2}$: 19.4 hours for rVWF and 16.6 hours for rVWF:rFVIII; IR: 1.8 U/dL per IU/kg infused for both rVWF and rVWF:rFVIII; mean residence time (MRT): 26.7 hours for rVWF and 25.2 hours for rVWF:rFVIII). FVIII levels increased substantially with a median peak at 24 hours of 111.0 U/dL for rVWF:rFVIII and 86.0 U/dL after rVWF alone, indicating that rVWF (vonicog alfa) induces a sustained increase in endogenous FVIII activity. The rVWF (vonicog alfa) PK profile was comparable at 50 IU/kg and 80 IU/kg VWF:RCo, and repeated PK at 80 IU/kg VWF:RCo showed close agreement between pretreatment and end-of-study results.

Further analysis of the PK data from the **071001** study supports the initial use of 50 IU/kg twice weekly for prophylaxis dosing in the present study for those subjects who are moving from on-demand to prophylaxis. Using 50 IU/kg for PK measurements, subjects in the **071001** study exhibiting a $T_{1/2}$ for rVWF of 14, 16, or 19 hours had rVWF plasma concentrations at 72 hours after administration of 2.55, 4.01, and 6.49% above baseline, respectively, and plasma concentrations at 96 hours after administration of 0.78, 1.40, and 2.71% above baseline, respectively. In this context it should be noted that subjects in the present study who have significant spontaneous bleeding while on twice weekly prophylaxis will have their regimen increased to 3 times per week based on clear criteria for different bleeding locations (for details see Section 8.6.4.3.1). Subjects in the present study who are switching from prophylaxis with a pdVWF product will begin on rVWF (vonicog alfa) using their same weekly total dose in IU/kg VWF:RCo used during their pdVWF prophylaxis divided into twice weekly infusions (for details see Section 8.6.4.3).

A total of 125 AEs occurred in 25/37 (67.7%) subjects (62/318 infusions [19.5%]) during or after infusion with IP. Of these, 116/125 were non-serious (all mild or moderate; none were severe), and 9 SAEs were reported in 7 subjects. Of 125 total AEs, 38 were temporally associated with IP; 8 AEs were considered causally related to IP: 6 non-serious related AEs (tachycardia, infusion site paraesthesia, electrocardiogram [ECG] t-wave inversion, dysgeusia, generalized pruritis, and hot flush) occurred in 4 subjects, and 2 related SAEs (chest discomfort and increased heart rate) occurred in 1 subject. No deaths occurred during this study.

None of the subjects developed anti-VWF or anti-FVIII neutralizing antibodies and no binding antibodies to VWF or rFurin, or antibodies against CHO protein or anti-Murine IgG were observed. No clinical or subclinical signs or symptoms of a thrombogenic event were observed in this study. Following an initial increase in ultralarge VWF multimers after administration of rVWF (vonicog alfa), a notable decrease in the proportion of large VWF multimers occurred between 12 and 24 hours post infusion, due to degradation by the endogenous ADAMTS13 followed by a continued decline until the end of the 96-hour follow-up period.

Overall, the data support the safe and effective use of rVWF (vonicog alfa) with or without rFVIII (ADVATE, octocog alpha) in the treatment of bleeds in patients with VWD.

6.5.2.4 Study 071101

This was a phase 3, prospective, open-label, multicenter clinical study to evaluate efficacy and safety of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) in elective surgical procedures in adult subjects with severe VWD. A total of 24 subjects were enrolled (signed informed consent) and screened, 15 subjects were treated with rVWF (vonicog alfa), and 15 subjects completed the study.

Eleven subjects underwent a PK assessment by infusion of 50 ± 5 IU/kg rVWF:RCo at an infusion rate of up to 4 mL/min. 12 to 24 hours before surgery, subjects received a dose of 40 to 60 IU/kg rVWF:RCo. Within 3 hours prior to surgery, the subject's FVIII:C levels were assessed with a target of 30 IU/dL for minor and oral surgeries and 60 IU/dL for major surgeries. Within 1 hour prior to surgery, subjects received a dose of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) (depending on the target FVIII:C levels at the 3 hour assessment). VWF and FVIII IR and $T_{1/2}$ for each subject, when known, were used to guide the initial dose and subsequent doses.

The primary outcome measure was the overall assessment of hemostatic efficacy assessed by the investigator (hemophilia physician) 24 hours after last perioperative IP infusion or at completion of day 14 visit, whichever occurred earlier, and was summarized by the percentage of subjects in each efficacy category ("excellent", "good", "moderate" and "none"). Point estimate and corresponding 90% two-sided exact CI was calculated for the rate of subjects with an overall assessment of hemostatic efficacy. All 15 subjects treated with rVWF (vonicog alfa) (with or without ADVATE) for major (10), minor (4), and oral (1) elective surgical procedures had overall hemostatic efficacy ratings of "excellent" or "good". Most (73.3%) subjects had "excellent" overall hemostatic efficacy ratings; of these, 7 underwent major surgery and 4 underwent minor surgery. The remaining 26.7% subjects had "good" overall hemostatic efficacy ratings: 3 underwent major surgery and 1 underwent oral surgery. All 8 subjects with VWD Type 3, the subtype classified as absolute VWF deficiency, had overall hemostatic efficacy ratings of "excellent" (87.5%) or "good" (12.5%).

Intraoperative hemostatic efficacy ratings were also rated as "excellent" or "good" for all 15 treated subjects. Most (86.7%) subjects had "excellent" intraoperative hemostatic efficacy ratings; of these, 8 underwent major surgery, 4 underwent minor surgery, and 1 underwent oral surgery. Two (13.3%) subjects who underwent major surgery had "good" intraoperative hemostatic efficacy ratings. Intraoperative hemostatic efficacy was rated as "excellent" or "good" for all subjects with VWD Type 3: "excellent" for 7 (87.5%) subjects and "good" for 1 (12.5%) subject.

Only 1 subject received an intraoperative dose of rVWF (18.1 IU/kg) and ADVATE (8.1 IU/kg). The median daily postoperative weight-adjusted dose of rVWF (vonicog alfa) (with or without ADVATE) was 23.5 IU/kg on postoperative Day 1 (n=3) and 25.5 IU/kg on postoperative Day 14 (n=2). In subjects treated with rVWF:ADVATE, the daily postoperative weight-adjusted dose was 16.9 IU/kg rVWF and 7.6 IU/kg ADVATE on postoperative Day 1 (n=1) and decreased to 50.8 IU/kg rVWF and 7.6 IU/kg ADVATE on postoperative Day 7 (n=1). For subjects treated with rVWF alone, the median weight-adjusted dose (Q1, Q3) of rVWF was 35.4 IU/kg on postoperative Day 1 (n=2) and decreased to 23.7 IU/kg on postoperative Day 7 (n=4) and 25.5 IU/kg on postoperative Day 14 (n=2).

A total of 11 subjects were evaluated for PK in the study. As expected, postinfusion increases in concentrations of VWF:RCo, VWF:Ac, VWF:Ag, and VWF collagen binding (VWF:CB) were observed. Mean values for VWF:RCo were as follows: AUC0-∞/dose was 37.50 hours*IU/dL per IU/kg infused; AUC0-72h/dose was 34.08 hours*IU/dL per IU/kg infused; T1/2 was 17.83 hours; MRT was 24.32 hours; CL was 0.03117 dL/hour/kg; and volume of distribution at steady state (Vss) was 0.6837 dL/kg. Median values for VWF:RCo were as follows: AUC0-∞/dose was 32.94 hours*IU/dL per IU/kg infused; AUC0-72h/dose was 31.70 hours*IU/dL per IU/kg infused; T1/2 was 14.62 hours; MRT was 21.80 hours; CL was 0.03036 dL/hour/kg; and Vss was 0.7078 dL/kg. The VWF:RCo activity was consistent with that previously observed in clinical studies 071001 and 070701.

rVWF (vonicog alfa) was safe and well tolerated in adults with severe VWD undergoing major, minor, and oral elective surgical procedures. Of the 12 total treatment-emergent AEs (TEAEs) that occurred during the study, 2 deep vein thrombosis events (1 non-serious and 1 serious, as a part of one case) reported in one subject, who underwent total hip replacement surgery and who had concurrent condition of obesity, was assessed by the sponsor as possibly causally-related to study treatment. None of the TEAEs were either a severe allergic or hypersensitivity reaction or developed due to a severe allergic reaction.

One subject with VWD Type 3 who had an intraoperative transfusion of packed red blood cells during total knee replacement surgery tested positive for binding antibodies to VWF on postoperative Day 7 through study completion. No subjects developed neutralizing antibodies to rFVIII or binding antibodies to CHO, rFurin, or murine IgG.

In summary, the data support the safe and effective use of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) in achieving intra- and post-operative hemostasis in adult subjects with severe VWD undergoing major, minor, and oral elective surgical procedures.

6.5.2.5 Study 071401: Single Subject with von Willebrand Disease

One subject who exhibited allergic reactions to currently marketed pdVWF products was treated in the single-subject study **071401** with rVWF (vonicog alfa) only for the bleed treatment of continued hematuria, and for biopsy and surgical resection of a left-kidney mass.

For the initial rVWF (vonicog alfa) infusion, the subject received a test dose of 5% of the total dose of 60 IU/kg rVWF:RCo at an infusion rate of 1 mL/min. After a 10 to 15-minute observation period, no adverse symptoms or signs were noted and the subject received the remaining 95% of the total dose. The subject was monitored for any signs of an allergic reaction, and none were noted. Treatment with rVWF (vonicog alfa) every 12 to 24 hours was to continue at the discretion of the investigator based on VWF levels and clinical symptomatology. The subject had an excellent response and recovery, which allowed for daily dosing of rVWF (vonicog alfa) and, within 24 hours, the subject's bleeding had stopped. Daily dosing of rVWF (vonicog alfa) was maintained and the subject received his last dose on [redacted].

The subject also received rVWF (vonicog alfa) for 7 days for prophylaxis for surgery (surgical resection of a left-kidney mass). The subject experienced no hemorrhagic complications and no AEs that were considered related to the use of rVWF (vonicog alfa).

6.6 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

Current treatment of VWD patients relies on desmopressin and VWF products manufactured from pooled human plasma. Human VWF produced by recombinant technology could offer a new perspective in treatment of VWD. The benefit for the individual subject is anticipated to be significant during this clinical study. He/she may benefit from a product that minimizes excessive FVIII administration and thus allowing individualized dosing of VWF at optimal levels. Variations in VWF multimeric composition may lead to variability with respect to treating or preventing bleeds in VWD subjects, especially mucosal bleeds which are especially problematic. rVWF (vonicog alfa) product manufactured by Baxalta consistently contains ULMW VWF multimers due to the fact that the product has not been exposed to ADAMTS13.

The initial presence of these ULMW VWF multimers, which are subsequently cleaved by the subject's endogenous ADAMTS13, may result in improved platelet and collagen binding and therefore provide more predictable treatment outcomes.

By using a recombinant product, the risk of transmission of adventitious agents and other blood-borne pathogens associated with the use of products of human or animal origin has been eliminated. At this stage of product development, the key societal benefit is a better understanding of advanced treatment options for VWD and enhanced product availability.

These benefits outweigh the following identified or potential risks of rVWF (vonicog alfa):

- allergic-type hypersensitivity reactions as with any intravenous protein product
- the occurrence of thromboembolic events
- the development of neutralizing antibodies to VWF

Refer to the IB for further details on benefits and risks of the IP.

6.7 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996, with Addendum E6(R2) dated Nov 2016 EMA/CHMP/ICH/135/1995), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives 2001/20/EC and 2005/28/EC, the Declaration of Helsinki and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

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

7.2 Primary Objective

The primary objective of this study is to prospectively evaluate the 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.

7.3 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 FVIII activity

7.4 Exploratory Objectives

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

8. STUDY DESIGN

8.1 Overall Study Design

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

Subjects transitioning from on-demand treatment (OD subjects) or subjects switching from prophylactic treatment with pdVWF (pdVWF switch subjects) will receive prophylactic treatment with rVWF (vonicog alfa) for a 12-month period. The dose will be 50 ± 10 IU/kg rVWF twice weekly for OD subjects or will be based on their prior pdVWF dose for pdVWF switch subjects, and 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 Section 8.6.4.3).

The overall duration of prophylactic treatment with rVWF per subject will be 12 months.

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 Section 8.6.4.4.2).

The overall study design is illustrated in Figure 1.

8.2 Duration of Study Period(s) and Subject Participation

The overall duration of the study is approximately 27 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The subject participation period is approximately 15 months from enrollment to completion (i.e, last study visit), unless the subject is prematurely discontinued.

8.3 Outcome Measures

8.3.1 Primary Outcome Measure

8.3.1.1 Efficacy

- Annualized bleeding rate (ABR) for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa)

8.3.2 Secondary Outcome Measures

8.3.2.1 Additional efficacy of Prophylactic Treatment with rVWF (vonicog alfa)

- ABR percent reduction success for OD subjects defined as at least 25% reduction of ABR for spontaneous (not related to trauma) bleeding episodes during rVWF (vonicog alfa) prophylaxis relative to the subject's own historical ABR during on-demand treatment
- ABR preservation success for pdVWF switch subjects 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 during prophylactic treatment with pdVWF
- Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 bleeding episodes during the 12-month 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
- Spontaneous ABR 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)

8.3.2.2 Safety

- AEs: incidence, severity, causality
- Thromboembolic events
- Hypersensitivity reactions
- Development of neutralizing antibodies to VWF and FVIII
- Development of total binding antibodies to VWF and FVIII
- Development of binding antibodies to CHO proteins, mouse immunoglobulin G (IgG) and rFurin
- Clinically significant changes in vital signs and clinical laboratory parameters relative to baseline

8.3.2.3 Pharmacokinetics (PK) and Pharmacodynamics (PD)

- PK parameters after a washout for on-demand subjects: incremental recovery (IR), $T_{1/2}$, 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 VWF:Rco activity, VWF:Ag, VWF:CB activity.
- PD parameters after a washout for on-demand subjects: C_{max}, T_{max}, and $AUC_{0-tlast}$ as measured in FVIII activity by the 1-stage clotting assay (FVIII:C).
- PK parameters at steady state for on-demand and switch subjects: area under the concentration versus time curve from 0 to end of the partial dosing interval ($AUC_{0-tau;ss}$), 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. PK parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.
- PD parameters at steady state for on-demand and switch subjects: $AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$ as measured in FVIII activity by the 1-stage clotting assay. PD parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.
- Time course of FVIII clotting activity (FVIII:C) levels.

8.3.3 Exploratory Outcomes Measures

8.3.3.1 [redacted]

- [redacted]
- [redacted]

[redacted]

8.3.3.2 [redacted]

[redacted]

8.3.3.3 [redacted]

[redacted]

8.3.3.4 [redacted]

[redacted]

8.4 Randomization and Blinding

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

8.5 Study Stopping Criteria

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 (eg, 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.

The sponsor ultimately 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.

8.6 Investigational Product(s)

8.6.1 Packaging, Labeling, and Storage

8.6.1.1 rVWF (Recombinant von Willebrand Factor, vonicog alfa)

rVWF (vonicog alfa) will be packaged in boxes with 2 glass vials, one containing the rVWF powder, and the second vial containing the diluent (water for injection). Further details are provided in the IB and Pharmacy Manual. The rVWF label will include, at a minimum, the actual VWF:RCo potency and the date of expiration.

rVWF (vonicog alfa) is a powder that should be stored refrigerated (2-8°C [36-46°F]) . Deviations from the storage condition have to be communicated and followed up with the sponsor. Inadequately stored product will have to be placed in quarantine and may only be used after written IP administration authorization by the sponsor. After removal of the product from the refrigerator the product must not be returned to the refrigerator. The reconstituted product has to be used immediately (at least within 3 hours). rVWF (vonicog alfa) must not be used beyond the expiration date printed on the vial label. Avoid freezing at all times.

8.6.1.2 rFVIII (Recombinant Factor VIII, octocog alfa /ADVATE)

ADVATE (rFVIII, octocog alfa) will be packaged in boxes with 2 glass vials, one containing the lyophilized rFVIII, and the second vial containing the diluent. Further details are provided in the IB and Pharmacy Manual. The ADVATE label will include, at a minimum, the actual FVIII:C potency and the date of expiration.

ADVATE (rFVIII, octocog alfa) should be refrigerated (2-8°C [36-46°F]) in powder form and should not be used beyond the expiration date printed on the vial.
Deviations from the storage condition have to be communicated and followed up with the sponsor. Inadequately stored product will have to be placed in quarantine and may only be used after written IP administration authorization by the sponsor. After removal of the product from the refrigerator the product must not be returned to the refrigerator and has to be used immediately. Avoid freezing at all times.

8.6.2 Reconstitution

The reconstitution procedures for both rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) products are detailed in the Pharmacy Manual.

8.6.3 Administration

Following reconstitution, rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) (in case of bleeding episode treatment) should be administered to study subjects at room temperature and within 3 hours of reconstitution. The reconstituted rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa), should be inspected for particulate matter and discoloration prior to administration, whenever the solution and container permit. The solution should be clear and colorless in appearance. If not, do not administer the product. Plastic syringes provided by the sponsor must be used since coagulation factors tend to stick to the surface of glass syringes.

Investigational product infusions should be given at a slow enough rate to ensure the subject's comfort. The rate should not exceed 4 mL/minute The investigator/ subject shall ensure that no visible residual volume remains in the syringe(s) and that the complete content is administered. Upon completion of the infusion, the butterfly catheter should be flushed with at least 2 mL of saline solution. In case of a (central) venous access device, the flush should be with at least 10 mL of saline solution. The IP infusions should be administered over a duration of 2 to 20 minutes, depending on the volume.

Only the actual potencies of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) as stated on the vial labels and described in the Pharmacy Manual should be used.

A variation of up to 10% of the intended dose for prophylactic infusions and of the intended dose for treatment of bleeding episodes is permissible and the exact dose should be recorded on the Case Report Form (CRF). Using of partial vials is not allowed.

At study visits where recovery analysis is being done, vials with the same lot numbers should be used throughout the PK IP infusion per subject.

For treatment of bleeding episodes, sequential administration will be done: separate syringes of the appropriate dose of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) will be prepared for sequential infusion. rVWF (vonicog alfa) should be infused first sequentially followed preferably within 10 minutes by infusion of ADVATE (rFVIII, octocog alfa). Only the actual potencies of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) as stated on the vial labels and described in the Pharmacy Manual should be used.

The final dose of rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) should be at a ratio of 1.3:1 ± 0.2.

8.6.4 Description of Treatment

8.6.4.1 PK-Assessment Treatment

For on-demand subjects, two PK assessments will be performed: an initial PK assessment after a follow up visit and a steady state PK assessments at the end of the study. The IP infusion for the initial PK assessment is scheduled on the baseline visit, which should be within 42 days after the completion of screening procedures and confirmation of eligibility. At the baseline visit the subjects will receive a dose of 50 ± 5 IU/kg rVWF:RCo for PK assessment. 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). A washout period of at least 5 days is required prior to infusion of rVWF (vonicog alpha) for PK assessment. The 2nd PK assessment for on-demand subjects will be performed at steady state at the end of the study(see Section 11.6). Subjects previously enrolled in rVWF studies **070701**, **071001** or **071101** and having previously undergone PK assessments in these studies are required to repeat the PK assessment due to different dose and time points used in these former studies.

For pdVWF switch subjects, two steady state PK assessments will be performed. The 1st PK will be assessed shortly after reaching steady state, which is expected to be 11 days after the 1st prophylactic dose for majority of the subjects, around the prophylactic dose #5-6. The 2nd PK will be at the end of the study.

For steady state PK, 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) as long as it won't interfere with subject's the normal dosing schedule, otherwise the 96 hr sampling can be omitted (see Section 11.6). Final sample for PK analysis should be taken before next dose is administered.

8.6.4.2 Prophylaxis Initiation Treatment

The rVWF (vonicog alfa) prophylaxis initiation treatment visit will coincide with the 96 ± 2 h initial PK assessment for on-demand subjects. For pdVWF switch subjects, the rVWF (vonicog alfa) prophylaxis initiation treatment visit should occur within 42 days after the completion of screening procedures and confirmation of eligibility. At this visit subjects will receive their prophylaxis initiation dose. The prophylaxis doses are described in Section 8.6.4.3.

The subject will be trained on IP reconstitution and administration and may then qualify for home treatment (see Section 8.6.4.3.2). Refer toTable 6 (a/b) for study procedures and Table 8 (a/b) for clinical laboratory assessments.

8.6.4.3 Prophylaxis Treatment

For on-demand subjects, the standard prophylactic dose is 50 ± 10 IU/kg rVWF:RCo, which may be increased up to 80 IU/kg. All on-demand subjects will initially receive rVWF (vonicog alfa) twice per week (Table 1, Schedule A). Examples of all dosing schedules are provided in Table 1.

For pdVWF switch subjects, the weekly dose (IU/kg) of IP for each patient 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 (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 (Table 1, Schedule B). A once weekly dose regimen will be allowed after switch to rVWF (vonicog alfa) only if the patient has been on a once weekly dose regimen with pdVWF.

Table 1
rVWF (vonicog alfa) Dosing Schedule Examples: Schedules A and B

Example	M	T	W	Th	F	Sat	Sun	M	T	W	Th	F	Sat	Sun
Schedule A	X				X			X				X		
Schedule B	X		X			X		X		X			X	

The prophylaxis dose may be further individualized within the range based on:

- available historical PK data
- type and severity of bleeding episodes the subject has experienced in the past and
- monitoring of appropriate clinical and laboratory measures

The individualized prophylaxic dose assignment will have to be agreed with the sponsor in advance, and the rationale should be well documented.

8.6.4.3.1 Adjustment of Dose or Dose Interval

In general, the dose and/or dose interval for each subject should not be changed unless prompted by clear medical needs. Dose and frequency adjustments should be agreed with the sponsor in advance unless it constitutes an urgent safety measure. The rationale for dosing adjustments needs to be documented in the subject's medical record.

For both OD and switch patients, dose escalations (not exceeding the upper dose limit of 80 IU/kg rVWF:RCo) and increase of dose frequency will only be allowed in case of insufficient therapeutic response with breakthrough bleeding episodes. The criteria for dose and/or frequency escalation are specific to each bleeding indication but, overall, involve 1 significant breakthrough bleeding episode despite the subject being compliant with scheduled prophylaxis treatment. For switch patients who require a dose escalation due to a breakthrough bleed, the frequency should be kept the same but the dose (IU VWF:RCo per infusion) should be increased up to 80 IU VWF:RCo. Following that, increases in frequency may be considered upon consultation with the Sponsor. For on demand subjects who require a dose escalation, at the discretion of the PI upon consultation with the Sponsor, the frequency may be kept the same but the dose (IU VWF:RCo per infusion) should be increased up to 80 IU VWF:RCo. If this proves to be insufficient, then the dosing frequency may be increased in these subjects. Table 2 presents the criteria for dosing escalation per each bleeding indication taken 50 ± 10 IU VWF:RCo/kg twice weekly dose as an example of subject's assigned starting dose. The criteria are applicable for both OD and switch subjects who were initially assigned to twice weekly dosing. Subjects entering the study will begin prophylaxis treatment according to Schedule A (Table 1) and will remain at this dose and frequency until meeting the criteria for escalation to the next higher schedule: for example, from 2 infusions of 50 ± 10 IU VWF:RCo/kg/week to 3 infusions of 50 ± 10 IU VWF:RCo/kg/week (Schedule B) to achieve an adequate therapeutic response. If a subject started with a weekly dose (possible for switch subjects), similar criteria would apply except that the subject will be excalated to twice weekly dosing if frequency change is necessary.

Table 2
Criteria for Escalation Specific to Each Bleeding Indication

	Schedule A	Schedule B
Joint bleeding	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a spontaneous joint bleeding episode occurs while on this regimen, the subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B following its resolution	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
GI bleeding	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a severe GI bleeding episode, i.e., requiring red blood cell transfusion, occurs while on this regimen, the subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B following its resolution	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Menorrhagia	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) on days 1 and 2 of menses for 2 cycles. Menstrual flow will be monitored by the PBAC score. If the average pictorial chart score is > 185, then the subject will escalate to up to 80 IU/kg or, if necessary, to Schedule B	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) on days 1, 2, and 3 of menses. Menstrual flow will be monitored by the PBAC score.
Epistaxis	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. The subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B in the event of 1 occurrence of breakthrough bleeding requiring intervention such as iron replacement therapy, transfusion, packing, hospitalization; or 2 bleeding events that require treatment with factor replacement	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Oral and Other Mucosa	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. The subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B in the event of 1 occurrence of breakthrough bleeding requiring intervention such as iron replacement therapy, transfusion, packing, hospitalization; or 2 bleeding events that require treatment with factor replacement.	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Muscle and Soft Tissue	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a spontaneous bleeding episode occurs while on this schedule, the subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B following its resolution.	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.

Abbreviations: GI: gastrointestinal; PBAC: Pictorial Blood Assessment Chart.

If a subject does not adequately respond to rVWF (vonicog alfa) therapy, he/she will be evaluated for the presence of neutralizing and total binding anti-VWF antibodies (see Section 12.9.3.2).

If a subject experiences a bleed while receiving rVWF (vonicog alfa) three times per week, the investigator should treat the bleed with rVWF (vonicog alfa) at doses up to 80 IU VWF:RCo/kg at a frequency determined by the investigator until the bleed resolves. Upon resolution of the bleeding event, the subject will return to their assigned prophylaxis regimen.

It is essential for the success of this study that the subjects adhere to treatment regimens. Therefore, procedures for monitoring subject's compliance are implemented (see Section 10.7).

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. For example, a subject routinely infuses IP on Monday and Thursday, he/she misses the Monday time point and therefore may infuse the IP on the next day (Tuesday) and thereafter proceed with infusing the IP on Thursday (considering a minimum 12 hours between the infusions) and return to the initial schedule.

If more than 30% of infusions of IP are missed within the visit interval of 3 months the subject will be discontinued from the study (see Section 9.4).

8.6.4.3.2 General Instructions for Home Treatment for Prophylaxis

At the discretion of the investigator, a subject may be considered suitable for home treatment only after the subject has received at least 1 infusion of IP in the clinic, either during planned prophylactic IP exposure or during the treatment of bleeding episodes, and meets the following additional criteria:

1. Fully understands the concept of a clinical study and related documentation (documented training of at least 30 minutes),
2. Has a history of previous experience with home treatment including self-administration and treatment with VWF containing concentrates,
3. Has adequate time for initial training of the study drug preparation (preparation, mixing and infusion of the IP(s) (documented training of at least 30 minutes).

This applies both to subjects who were on prior on-demand treatment and to subjects switching form prophylaxis with pdVWF. In the event a healthcare professional is required to administer IP, he/she must be trained and qualified by the investigator on the above procedures prior to the decision for home treatment. A Subject Guideline detailing all instructions and information listed above will be provided to each subject.

8.6.4.4 Treatment of Bleeding Episodes

8.6.4.4.1 General Instructions for Home Treatment of Bleeding Episodes

If a subject experiences a bleeding episode, he/she should contact the study site immediately and the site investigator should provide instructions on the treatment regimen. If the subject initiates the treatment at home, he/she should at least follow up with the study site if a visit is needed as per the standard of care at the center.

In the event a healthcare professional is required to administer treatment at the subject's home, he/she must be trained and qualified by the site investigator on the above procedures prior to the decision for home treatment. Once a subject has received 1 infusion of rVWF (vonicog alfa) in the clinic (either during planned IP exposure or during the treatment of a bleeding episode) and meets the criteria for home treatment, the treatment of bleeding episodes with IP can be conducted at home (see Section 8.6.4.3.2).

If a subject is not qualified for home treatment, rVWF (vonicog alfa) infusions must be administered at the study site.

If a subject experiences a bleeding episode that requires treatment between the screening and the prophylaxis initiation visit, the subject will be treated with IP (rVWF with or without ADVATE). Treatment with IP must occur at the study site unless the subject has previously qualified for home treatment with rVWF (vonicog alfa). If rVWF (vonicog alfa) treatment is not feasible, the subject may use his/her standard of care, such as commercial pdVWF/FVIII products. In any case a washout period of at least 5 days is required prior to rVWF (vonicog alfa) PK infusion at the initial PK assessment visit for on-demand subjects.

If a subject experiences a bleeding episode requiring treatment during the PK assessment, rVWF (vonicog alfa) should be used to treat the bleed. Blood draws for PK assessment will be stopped and the PK assessments will be repeated once the bleed has resolved and the subject is free of any symptoms related with the bleeding episode. Dose and frequency of rVWF (vonicog alfa) infusions or any other replacement therapy to stop the bleed should be recorded in the electronic Case Report Form (eCRF), and the reason for the use of any non-IP product or therapy should be documented.

8.6.4.4.2 Dosing Recommendations for Treatment of Bleeding Episodes

If an acute bleeding episode occurs, the subject will be treated with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa). It is the sponsor's opinion that, in many cases, treatment with ADVATE (rFVIII, octocog alfa) may not be necessary, since rVWF (vonicog alfa) prophylaxis will serve to increase endogenous FVIII levels. However, if endogenous FVIII is below 30-40 % or is unknown and cannot be estimated from the subject's PK study, an infusion of rVWF: ADVATE at an rVWF: ADVATE ratio of 1.3:1± 0.2 should be administered initially. Subsequent infusions should be with rVWF:RCo 40 to 60 IU/kg with or, in many cases,without 30 to 45 IU/kg ADVATE (only to be administered if plasma FVIII levels fall below 30 IU/L during the treatment period). Dosing may be adjusted downward or upward up to 80 IU/kg rVWF at the treating physician's discretion based upon the subject's prior history, PK and other factors.

If FVIII levels are not available, dosing is at the discretion of the investigator based upon the individual subject's PK data. Using ADVATE (rFVIII, octocog alfa) in addition to rVWF (vonicog alfa) in subsequent doses carries the risk of an excessive rise in FVIII:C. Therefore, reduced doses of ADVATE (rFVIII, octocog alfa) and/or prolongation of the dose interval should be considered.

The following is general guidance and the sponsor's suggestion for treatment of breakthrough bleeds, however each PI will determine the treatment based on the local acceptable practice how to monitor and adjust treatment for a bleeding episode. An effort should be made to discuss with the sponsor (or sponsor's delegate) the treatment strategy.

In general the aim of the initial dose should be full replacement of VWF with VWF:RCo levels of >0.6 IU/ml (60%) and FVIII:C of >0.4 IU/mL (40%). In major bleeding episodes, subsequent doses should keep the trough level of VWF:RCo >50% for 3 days and then as deemed necessary by the investigator for subsequent days. In moderate bleeding episodes, the dose and trough level may be reduced to >30% for as long as deemed necessary by the investigator. Treatment for minor bleeding episodes will generally consist of only 1 or 2 doses of rVWF (vonicog alfa) IP.

If the VWF:RCo level is above 150%, a planned treatment should be delayed by at least 12 hours; if the VWF:RCo level is above 200%, a planned treatment should be delayed by at least 24 hours. In either case, a lower subsequent dose (e.g., 20 IU/kg VWF:RCo) may be appropriate.

Dosing recommendations are listed in Table 3.

Dosage must be individualized based on the subject's weight, VWD type, and the severity of the bleeding episode, as well as on monitoring of appropriate clinical and laboratory measures. In the phase 1 study **070701**, 1.0 IU/kg VWF:RCo raised the circulating level of VWF:RCo by 0.017 IU/mL (1.7 %). In the same study, the observed mean half-life for rVWF (vonicog alfa) was 19.3 hours, with a standard deviation of 10.9 hours.

Table 3
rVWF:RCo Dosing Recommendations for the Treatment of Bleeding Episodes Due to VWD

Classification of VWD	Hemorrhage	Dosage (IU VWF:RCo/kg BW)
Type 1 • Severe (Baseline VWF:RCo activity typically <20%)	Minor (e.g., epistaxis, oral bleeding, menorrhagia[a])	40 to 50 IU/kg (1 or 2 doses)
	Major (e.g., severe or refractory epistaxis, menorrhagia*, GI bleeding, CNS trauma, hemarthrosis, or traumatic hemorrhage)	Initial dose 50 to 75 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment
Type 2 (all variants) and Type 3	Minor (clinical indications above)	40 to 50 IU/kg (1 or 2 doses)
	Major (clinical indications above)	Initial dose of 60 to 80 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment

[a] Menorrhagia is defined as excessive bleeding during menstruation. A diagnosis of menorrhagia will be defined by a prospectively completed Pictorial Blood Assessment Chart (PBAC) score >185 and normal cervical cytology or requiring use of a VWF-containing concentrate for treatment of excessive menstrual bleeding for at least one menstrual cycle during the prior year.

Variances of up to 10% in dosing are permissible during treatment of bleeding episodes, but rounding to the nearest vial size should be avoided.

Subjects with non-neutralizing binding anti-VWF antibodies should initially be treated with a dose known to be efficacious based on the subject's medical treatment history which may differ from the recommendations provided in Table 3. Subjects should be monitored for lack of efficacy as well as for FVIII (mandatory), VWF:RCo (mandatory), and VWF:Ag (optional where testing is not available) levels after 3 to 6 hours. Re-dosing with rVWF (vonicog alfa) in combination with ADVATE (rFVIII, octocog alfa) using the same (initial) dose and adaptation of the dosing frequency should be considered until cessation of the bleed, if the FVIII and/or VWF:RCo levels drop below 30%-50% depending on bleeding severity.

The number of subsequent infusions and the dosage levels prescribed will be determined by the investigator on the basis of the clinical severity, response to current therapy, available laboratory data, and the subject's historical treatment for similar bleeding episodes.

8.6.4.5 Treatment of Surgical Bleeding

Subjects enrolled in this study who require surgery or dental procedures will be treated with IP to manage their surgical bleeding then afterwards will resume their prophylactic rVWF (vonicog alfa) treatment schedule. Subjects who at time of screening have an already scheduled surgical intervention are not eligible for participation in the study.

8.6.4.5.1 Major, Minor and Oral Surgery Definition

The following definitions and criteria are used to serve as a guidance for *major, minor and oral surgery*.

Major surgeries generally refer to major orthopedic surgery (e.g., joint replacement, arthroscopic or open synovectomy, arthrodesis, hardware removals like plates or intramedullary nails, etc.), major abdominal surgery (e.g. open or laparoscopic hernioplasty, cholecystectomy, colon or small bowel resection, etc.), major gynecological surgery (e.g. open or laparoscopic myomectomy, hysterectomy, removal of endometriosis, polyps, cysts, adhesiolysis, etc.), major head and neck surgery (e.g.: tonsillectomy, adenoidectomy, rhinoplasty, lymphadenectomy, thyroidectomy, parotidectomy. etc.), any intracranial , cardiovascular or spinal surgery and any other surgery which has a significant risk of large volume blood loss or blood loss into a confined anatomical space. Extraction of impacted third molars is generally also considered major surgery due to the expected difficulty of surgery and the expected blood loss.

Minor surgeries generally refer to interventions such as placement of intravenous access devices, removal of small skin lesions, arthroscopy, gastroscopy, colonoscopy or conisation.

Oral surgeries comprise extractions of fewer than three teeth, if the teeth are non-molars and have no bony involvement.

A summary schedule of visit assessments and laboratory sampling is included in Supplement tables in Section 20.2.1 and Section 20.3.1.

8.6.4.5.2 Preoperative Priming Dose

12- 24 hours prior to surgery, a priming dose with rVWF (vonicog alfa), using the rVWF IR and $T_{1/2}$ for this subject , will be infused to allow the endogenous FVIII levels to raise to at least 30 IU/dL (minor, oral surgery), or 60 IU/dL (major surgery) at the time of the loading dose of rVWF (vonicog alfa) is infused.

As a general guidance a priming dose of 40-60 IU/kg rVWF:RCo will be administered. If not assessed prior to the preoperative priming dose, a IR recovery may be calculated for subjects undergoing minor and oral surgery.

8.6.4.5.3 Preoperative Loading Dose

An rVWF (vonicog alfa) loading dose should be administed within 3 hours before surgery. VWF and FVIII levels should be assessed within 3 hours prior to surgery initiation and results must be available prior to administering the loading dose. If FVIII levels prior to loading dose administration are not at least 30 IU/dL (minor, oral surgery), or 60 IU/dL (major surgery) ADVATE (rFVIII, octocog alfa) will be administered in addition to rVWF (vonicog alfa) in order to raise FVIII:C levels to recommended levels.

The preoperative loading dose will be calculated as the difference in the target peak and baseline plasma VWF:RCo levels divided by the IR (ΔVWF:RCo x BW (kg) /IR). The PK results will be provided prior to the planned surgery. If the IR is not available, assume an IR of 1.7 IU/dL per IU/kg and calculate the initial dose as follows: (100 − baseline plasma VWF:RCo) x BW (kg) / 1.7. For minor and oral surgery, the IR from the Preoperative Priming Dose visit will be used to guide dosing and the target peak is 50-60 IU/dL VWF:RCo and 40-50 IU/dL FVIII. For major surgery, the target peak is 100IU/dL VWF:RCo and 80-100 IU/dL FVIII.

The surgery may only start after normalization of the activated partial thromboplastin time (aPTT).

8.6.4.5.4 Intra- and Postoperative (maintenance) Dosing

After the preoperative loading dose(s), subjects who have not achieved the desired postinfusion recovery will continue to receive rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) as a bolus infusion, depending on VWF and FVIII levels. The peri- and post-operative substitution regimen will be individualized according to the PK results, intensity and duration of the hemostatic challenge, and the institution's standard of care.

Subjects undergoing minor surgery will be infused with rVWF (vonicog alfa) every 12-24 hours or every other day, targerting ≥30IU/dL (rVWF and FVIII) for at least the first 48 hours.

Subjects undergoing oral surgery will be infused with rVWF (vonicog alfa) at least once within the first 8-12 hours, targeting ≥30 IU/dL (rVWF and FVIII).

Subjects undergoing major surgery will be infused with rVWF (vonicog alfa) every 12-24 hours for at least the first 72 hours post-surgery, targeting a VWF:RCo and FVIII:C trough plasma level >50 IU/dL, followed by further treatment post-72 hours for as long as deemed necessary by the Investigator, targeting a VWF:RCo and FVIII:C trough plasma level of ≥30 IU/dL.

Dose modifications based on pre-infusion VWF/FVIII levels will be performed as needed. For subsequent infusions post surgery, in case pre-infusion levels are not available prior to the consecutive infusion in a timely manner, pre-infusion levels from the previous dose may be used by the investigator for dosing guidance.

Peak plasma level guidance is matching to Section 8.6.4.4.2

A schedule of all perioperative visit assessments and laboratory sampling can be found in supplement tables in Section 20.2.1 and Section 20.3.1.

8.6.4.6 Thrombosis Prophylaxis

Thromboembolic events have been reported in patients who have VWD, especially in the setting of known risk factors for thrombosis including low ADAMTS13 levels. Therefore, subjects who are at risk for developing thromboembolic events should be monitored for early signs of thrombosis, and prophylaxis measures against thromboembolism should be instituted according to current recommendations and standard of care. For all subjects who are VWD patients and are receiving VWF concentrate, attention should be given to avoid exceeding maximal recommended plasma activity levels of VWF:RCo (250 IU/dL) and FVIII (250 IU/dL).

Anticoagulation measures, such as heparin, are acceptable and should follow study site standards. The investigator will record the use and reasons for such measures/agents on the appropriate CRF.

8.6.5 Investigational Product Accountability

The investigator will ensure that the IP(s) is stored as specified in the Pharmacy Manual and that the storage area is secured, with access limited to authorized study personnel. All temperature excursions at the subject's home need to be monitored by the site (please refer to the pharmacy manual). The investigator will maintain records that the IP(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. The IP(s) must be dispensed only at the study site or other suitable location (e.g., infusion center; home, as applicable per study design), as specified in the protocol (see Section 10). Records will be maintained that includes the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

8.7 Source Data

Per ICH E6(R2) on GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). These may be in paper and/or electronic format. Source documents for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

No data will be entered directly onto the CRF.

For additional information on study documentation and CRFs refer to Section 17.2. The use of subject diaries is described in Section 10.5.

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding
   a. Type 1 (VWF:RCo <20 IU/dL) or,
   b. Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2M or,
   c. Type 3 (VWF:Ag ≤3 IU/dL).
2. Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.
3. For on-demand patient group, subject currently receiving on-demand treatment for whom prophylactic treatment is recommended by the investigator.
4. For pdVWF switch patient group, subject has been receiving prophylactic treatmentof pdVWF products for no less than 12 months prior to screening.
5. For on-demand patient group, subject has ≥3 documented spontaneous bleeds (not including menorrhagia) requiring VWF treatment during the past 12 months.
6. Availability of records to reliably evaluate type, frequency and treatment of bleeding episodes during at least 12 months preceding enrollment. Up to 24 months retrospective data should be collected if available. Availability of dosing and factor consumption during 12 months (up to 24 months) of treatment prior to enrollment is required for pdVWF switch subjects and is desired (but not a requirement) for on-demand subjects.
7. Subject is ≥18 years old at the time of screening and has a body mass index ≥18 but ≤30 kg/m^2.
8. If female of childbearing potential, subject presents with a negative blood/urine pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.[i]
9. Subject is willing and able to comply with the requirements of the protocol.

[i] Refer to Section 20.4 for a list of adequate contraceptive methods for females of childbearing potential.

9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

1. The subject has been diagnosed with Type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD (eg qualitative and quantitative platelet disorders or prothrombin time (PT)/international normalized ratio [INR] >1.4).
2. The subject is currently receiving prophylactic treatment with more than 5 infusions per week.
3. The subject is currently receiving prophylactic treatment with a weekly dose exceeding 240 IU/kg.
4. The subject has a history or presence of a VWF inhibitor at screening.
5. The subject has a history or presence of a FVIII inhibitor with a titer ≥0.4 Bethesda units (BU) (by Nijmegen modified Bethesda assay) or ≥0.6 BU (by Bethesda assay).
6. The subject has a known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins.
7. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
8. The subject has a medical history of a thromboembolic event.
9. The subject is human immunodeficiency virus (HIV) positive with an absolute Helper T cell (CD4) count <200/mm^3.
10. The subject has been diagnosed with significant liver disease per investigator's medical assessment of the subject's current condition or medical history or as evidenced by any of the following: serum alanine aminotransferase (ALT) greater than 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).
11. The subject has been diagnosed with renal disease, with a serum creatinine (CR) level ≥2.5 mg/dL.
12. The subject has a platelet count <100,000/mL at screening.
13. The subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to signing the informed consent.

14. The subject is pregnant or lactating at the time of enrollment.
15. Patient has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
16. The subject has participated in another clinical study involving another IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
17. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
18. The subject is scheduled for a surgical intervention.
19. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
20. The subject has a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
21. The subject is in prison or compulsory detention by regulatory and/or juridical order.
22. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.

9.3 Delay Criteria

1. If the subject has an acute bleeding episode or presents with an acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) the screening visit will be postponed until the subject has recovered.

9.4 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (i.e., reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the termination visit (including cases of withdrawal or discontinuation) are described in Section 10.6 and Section 20.2.

Discontinuation (i.e., complete withdrawal from study participation) may be due to dropout (i.e., active discontinuation by subject) or loss to follow-up (i.e., discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also will be withdrawn from treatment or discontinued from further study participation for the following reasons:

1. The subject is scheduled for an extended treatment period >3 months with non-topical immunomodulating drugs other than anti-retroviral chemotherapy (e.g., α-interferon, corticosteroid agents [equivalent to hydrocortisone greater than 10 mg/day]) during the course of the study.
2. Subjects with chronic hepatitis B or C develop ALT/AST levels exceeding 5 times the ULN for >1 month.
3. Subjects who experience severe hypersensitivity reactions, e.g., anaphylaxis upon exposure to rVWF (vonicog alfa).
4. Subjects who develop a neutralizing inhibitor to rVWF (vonicog alfa) and/or ADVATE (rFVIII, octocog alfa) (biological assays) that results in significant clinical effect, including but not limited to increasing the weekly dose of rVWF by ≥50%.
5. Subjects who demonstrate clinical signs of thromboembolic events.
6. The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through completion of the pregnancy and up to 1 year post delivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome.
7. The subject begins lactating. IP exposure will be discontinued. The investigator will record a narrative description of the course of the baby's development.
8. The subject is not compliant with the prophylactic treatment regimen and does not adhere to the frequency of IP administration. Once >30% of infusions are missed within a visit interval (3 months), the subject will be discontinued from further participation in the study.
9. The subject repeatedly uses other VWF products for prophylaxis or for the treatment of bleeding episodes in the absence of an acceptable justification to the sponsor.

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient who provides informed consent (i.e., signs and dates the informed consent form) is considered a subject enrolled in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (e.g., 071301) to be provided by the sponsor, 2- or 3-digit number study site number (e.g., 02) to be provided by the sponsor, and 3- or 4-digit subject number (e.g., 0003) reflecting the order of enrollment (i.e., signing the informed consent form). For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 071301-020003. All study documents (e.g., CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The study site is responsible for maintaining a screening log that includes all subjects who provided informed consent. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRF, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

The overall study design is illustrated in the Figure 1. Details on the procedures to be performed at each study visit, including screening, are provided in Supplement 20.2 "Schedule of Study Procedures and Assessments" and Supplement 20.3 "Clinical Laboratory Assessments".

10.3.1 Screening Visit

Written informed consent must be obtained from each subject before any study related procedures are performed. During the screening, site staff would be required to collect all details including date, location, type, severity and treatment received for all spontaneous and traumatic bleeding episodes occurring within the past 12 months. The maximum interval of bleed-free periods as well as trauma-induced bleeding episodes will also be recorded (prospectively and retrospectively). Study site personnel would be trained and qualified about which information should be obtained from diary, chart and pharmacy records, along with any other applicable site source documentation.

To initiate screening procedures, at least 72 hours must have elapsed since the last VWF administration for on-demand subjects and the subject must not be actively bleeding at the time of screening. For switch subjects, the usual interval between their pdVWF prophy infusions must have elapsed since the last VWF administration and the subject must not be actively bleeding at the time of screening. Multimer analysis and VWD gene mutation analysis should be performed at screening if not available in the subject's medical history.

The screening visit will be delayed if the subjects presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like symptoms, inflammatory diseases) until the event has resolved. All screening procedures and confirmation of eligibility shall take place within 42 days prior to the first infusion of IP. If the IP is not infused within 42 days, all screening assessments except blood group, human leukocyte antigen (HLA), genetics, multimeric pattern and [redacted], must be repeated to reconfirm eligibility. Refer to Supplement 20.2 and Supplement 20.3. Upon completion of screening procedures, subject eligibility will be confirmed by the sponsor on a subject eligibility form before additional study procedures are undertaken. The subject will maintain a diary that will include infusion logs (see Section 10.5). The allocation of IP will be initiated after the subject has qualified for home treatment (see Section 8.6.4.3.2).

In the event of a subject experiencing a bleeding episode that requires treatment between the screening visit and the subsequent visit (i.e. initial PK assessment visit for on-demand subjects or prophylaxis initiation visit for switch subjects), the subject will be treated with rVWF (vonicog alfa). If rVWF (vonicog alfa) is not available for any reason, e.g., subject not yet trained on IP administration, study site visit for IP administration not feasible, etc., the subject may use his/her standard of care, such as commercial pdVWF/FVIII products, and the reason for the use of non-IP products should be clearly documented.

10.3.2 Baseline Visit – Initial PK Assessment (On-demand Subjects Only)

After screening and confirmation of eligibility on-demand subjects will undergo an initial PK assessment. Subjects will receive a dose of 50 ± 5 IU/kg rVWF:RCo to determine VWF and FVIII levels. 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). See Section 20.2 and Section 20.3. IP infusion vials from the same lot number should be used for all PK-assessments per subject. Samples for measurement of FVIII and VWF activity taken through to 6 hours post-infusion will be obtained from an extremity different from that used for the infusion of IP.

Where needed, the phlebotomy site will be kept patent via an infusion of normal saline. In this event, at least 5 mL of blood will be collected and discarded before collection of the next test sample into a fresh syringe.

If the subject has a central venous catheter, the central line should be used to administer the infusion and a peripheral venipuncture should be used to collect the blood samples. In the event that a blood sample must be drawn through the central line used for administration of IP, the line must first be flushed with at least 10 mL normal saline or other suitable catheter flush solution that does not contain anticoagulant. At least 5 mL of whole blood must be collected and discarded prior to obtaining the sample.

If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.6.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment.

For pdVWF switch subjects, PK profile will not be assessed until reaching steady state after initiation of prophylaxis (see Section 10.3.4).

10.3.3 Prophylaxis Initiation Visit

The prophylaxis initiation visit will occur after the blood sample for the 96 hour PK assessment is drawn for on-demand subjects or within 42 days after screening and confirmation of eligibility for pdVWF switch subjects. The subject will receive the first rVWF (vonicog alfa) prophylactic dose of rVWF: RCo. Details on dose are provided in Section 8.6.4.3.

Procedures and assessments at this visit include (but are not limited to): AEs, bleeding episodes, medications taken, and non-drug therapies. Within 2 hours prior the IP infusion, a physical examination will be performed. Vital signs will be assessed within 30 minutes prior to IP rVWF (vonicog alfa) infusion and 30 minutes ± 15 minutes after IP infusion. Further details are provided in Supplement 20.2 and Supplement 20.3.

10.3.4 Initial Steady State PK-Assessment (pdVWF switch subjects only)

For pdVWF switch subjects, a full PK profile will be assessed at steady state conditions on two occasions. The initial PK assessment will be performed shortly after reaching steady state after starting prophylaxis dosing, which is suggested after 11 days post the 1st, around prophylaxis dose #5-6. The 2nd PK assessment at steady state will be performed at the end of the study.

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). In case the dosing schedule does not permit the 96 hr sampling, this sampling time point can be omitted (See Section 11.6). IP infusion vials from the same lot number should be used for all PK-assessments per subject.
Samples for measurement of FVIII and VWF activity taken through to 6 hours post-infusion will be obtained from an extremity different from that used for the infusion of IP. Where needed, the phlebotomy site will be kept patent via an infusion of normal saline. In this event, at least 5 mL of blood will be collected and discarded before collection of the next test sample into a fresh syringe.

If the subject has a central venous catheter, the central line should be used to administer the infusion and a peripheral venipuncture should be used to collect the blood samples. In the event that a blood sample must be drawn through the central line used for administration of IP, the line must first be flushed with at least 10 mL normal saline or other suitable catheter flush solution that does not contain anticoagulant. At least 5 mL of whole blood must be collected and discarded prior to obtaining the sample.

If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.6.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment. In case of surgery or bleeding, the PK assessment should be performed after 11 days after 1st prophylactic dose after re-start of prophylactic regimen. See Section 11.6 for more details.

10.3.5 Treatment of Bleeding Episodes

Treatment of bleeding episodes is described in detail in Section 8.6.4.4 and treatment of perioperative bleeding is described in detail in Section 8.6.4.5.

10.3.6 Perioperative Visits (only applicable if surgery is needed)

The perioperative visits from priming dose through postoperative day 14 will be required to check daily intra- and postoperative weight-adjusted dose of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa). Details on the procedures and assessments performed at each visit can be found in supplement tables in Section 20.2.1 and Section 20.3.1.

10.3.7 Follow-Up Visits (1 Month ± 1 Week, 2 Months ± 1 Week, 3 Months ± 2 Weeks, 6 Months ± 2 Weeks, 9 Months ± 2 Weeks post Prophylaxis Initiation Visit)

Visits will be performed after the prophylaxis initiation visit at 1 month ± 1 week, 2 months ± 1 week, and 3 months ± 2 weeks and thereafter every three months ± 2 weeks. Additional visits may occur if clinically indicated (see Section 10.3.8).

When possible, site visits should be scheduled on days when the subject is expected to infuse rVWF (vonicog alfa). Within 2 hours prior to the rVWF (vonicog alfa) IP infusion, a physical examination will be performed. Vital signs will be assessed within 30 minutes prior to IP infusion and 30 minutes ± 15 minutes after IP infusion. Incremental recovery (IR) will be determined at each follow-up visit based on VWF:RCo activity assessed prior to and after IP infusion.

The blood sample for IR analysis will be drawn within 30 minutes prior to IP infusion and 30 minutes ± 5 minutes after IP infusion. rVWF (vonicog alfa) will be infused at the regular prophylactic dose. For each subject's recovery analysis IP infusion, vials from the same lot number should be used.

Testing for VWF:RCo VWF:CB, rVWF:Ag, and FVIII:C level will be performed using the blood sample obtained before and after IP infusion.

The blood sample prior to IP infusion will also be used for the assessment of neutralizing and binding antibodies, clinical chemistry and hematology. For on-demand subjects, a washout period of at least 72 hours after the last infusion applies before the blood draw for the immunogenicity assays. For switch subjects, the wash out period may be reduced to the time interval between their pdVWF prophy infusions Bleeding episodes and the hemostatic efficacy will be evaluated based on the review of the patient diary. See Section 20.2 and Section 20.3. The evaluation of IP consumption and treatment compliance will be performed based on subject's diary entries. If a subject is not compliant with the prophylactic treatment regimen and does not adhere to the required frequency of administration of IP infusions (>30% of infusions were missed within a visit interval [3 months]) the subject will be withdrawn from the study.

At the 6 months ± 2 week visit an ECG will be performed and [redacted] data will be collected.

For the hemostatic efficacy assessment the following information will be recorded by the subject in the patient diary: bleeding location, type, severity, onset and resolution date and time, infusion date and time, clinical efficacy according to the rating scale.

If at any time during the study a subject's bleeding episode does not adequately respond to rVWF (vonicog alfa) therapy, he/she will be evaluated for the presence of neutralizing and total binding antibodies. Refer to Section 12.9.3.2.

Further guidance on completing the subject's diary will be provided to the subjects during training for home treatment (see Section 8.6.4.3.2).

10.3.8 Unscheduled Visits

For any unscheduled visit (except for collection of IP) a clinical assessment will be performed as per the scheduled follow-up visits with the exception of [redacted], ECG, and IR determination (refer to Supplement 20.2 and Supplement 20.3).

Subjects who have more than one bleeding episode in 3 months, or an increased frequency of bleeding, should go to the study site for an unscheduled visit.

Follow-up visits after the subject has experienced a bleed may be requested by the investigator. Additional assessments may be required which are at the discretion of the investigator.

10.3.9 End of Study PK Assessment and Study Termination Visit (12 Months ± 2 Weeks post Prophylaxis Initiation Visit)

At the 12 month ± 2 week visit, a full PK analysis at steady state will be performed for both cohorts: on-demand and switch subjects. 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) unless dosing schedule does not permit, in which case the 96 hr sampling can be omitted. If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.6.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment and the PK assessment should be performed after 11 days after 1st prophylactic dose after re-start of prophylactic regimen. See Section 11.6 for more details.

Refer to Supplement 20.2 and Supplement 20.3 for the other assessments to be performed at the PK assessment and study completion visits.

For on-demand subjects, a washout period of at least 72 hours is required between the PK infusion and the study termination visit (at the time of the 96 hour postinfusion PK assessment). For switch subjects, the wash out period may be reduced to the time interval between their rVWF (vonicog alfa) prophy infusions.Refer to Supplement 20.2 and Supplement 20.3 for the list of assessments to be performed at the termination visit.

Subjects will be offered the option to continue to receive rVWF (vonicog alfa) in a long-term continuation study.

10.4 Medications and Non-Drug Therapies

The following medications and non-drug therapies are **not** permitted within 30 days before study entry and during the course of the study:

Medications:

- 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) and an extended treatment period >3 months.
- Another investigational and/or interventional study drug (except rVWF and FVIII administered under the surgery protocol).

A subject who has taken any of these medications or received any of these non-drug therapies during the study will be withdrawn from the study.

The following medications are permitted during the course of the study:

- Antifibrinolytics (e.g., tranexamic acid, ε-amino caproic acid) or topical hemostats as needed, according to each institution's standard of care. These may be used, in accordance with local standard clinical practice, as the initial or only treatment for minor and moderate bleeding events. However, if the bleeding has not stopped within 24 hour following administration of this non-VWF treatment, infusion(s) with rVWF (vonicog alfa) should be started per protocol
- Emergent use of a VWF concentrate other than rVWF (vonicog alfa) may be permissible under certain circumstances (see Section 8.6.4.4.1)

Details of all adjunctive hemostatic medication used, including dose and reason for use, must be recorded in the eCRF.

10.5 Subject Diary

1. An electronic subject diary will be provided to each subject at the screening visit to record the following information:
    - IP infusions to include date, start and stop times of the infusion, number of vials utilized, and infusion volume for prophylactic treatment or treatment of spontaneous and traumatic bleeding episodes
2. Details of bleeding episodes (site, type, severity and date/time of bleeding) and response to treatment as described in Section 8.6.4.4
3. Subjective hemostatic efficacy assessments
4. Untoward events/unwanted experiences
5. Concomitant medications (including immunizations) and non-drug therapies
6. Patient Reported Outcomes (PROs)

Subjects and/or their legally authorized representatives will be trained on use of the diary. The diary will be provided in electronic format and remain with the subject for the duration of the study. The investigator will review the diary for completeness and request missing information periodically and in a timely manner. The investigator will record/capture any unwanted experience reported by the subject which may qualify as an AE on the AE eCRF.

Infusions performed at the study site will first be recorded in the site's source documents and not in the patient diary.

Subject entries in the diary will serve as source records. During study participation the investigator has access to the database holding the subject diary data. After study closure, the investigator will receive the diary records for their subjects, including audit trail records, in PDF format. The data will be transmitted to the CRF by a validated transfer.

Paper diary may be utilized in rare case where electronic diary use is not possible.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have completed all study procedures according with the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, AE (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, e.g., technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the study termination visit. If the termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the termination visit.
If a subject terminates participation in the study and does not return for termination visit, his/her last recorded assessments shall remain with the last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.2 Schedule of Study Procedures and Assessments and Supplement 20.3 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

10.7 Procedures for Monitoring Subject Compliance

Subject compliance with the procedures of this study (treatment regimens and study visits) will be monitored by the investigator or/a licensed healthcare professional at the study site.

During the regular scheduled follow-up visits a direct review of the subject's source data (e-diaries) will be performed at the sites and evaluated against the protocol requirements. In addition drug accountability will be evaluated at each follow-up study visit and the study termination visit by comparing the infusions recorded in the subject diary with empty vials returned by each subject to the study site, and the study site's dispensing record. Protocol deviations will be noted in the final report.

11. ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

11.1 Assessment of Spontaneous Bleeding Episodes/Annualized Bleed Rate

The annualized bleed rate (ABR) will be assessed based upon each individual spontaneous bleed, requiring coagulation factor replacement therapy, i.e., rVWF (vonicog alfa) treatment. The following details on bleeding episodes will be recorded by the subject in the electronic diary (for home treatment), the subject's healthcare provider in the site's source documents (for treatments away from the primary investigative site), or by authorized, qualified personnel at the participating site in the subject's medical records (for hospital-based treatment):

- Location of bleed; i.e., joint, menorrhagia, epistaxis, gastrointestinal, soft tissue, muscle, body cavity, intracranial, etc.
- Type of bleed; i.e., spontaneous, traumatic, unknown
- Severity of bleed; i.e., minor, moderate, and major (see Table 3)
- Date and time of onset of bleed
- Date and time of each infusion of rVWF (vonicog alfa) or rVWF (vonicog alfa)-ADVATE (rFVIII, octocog alfa) used to treat a bleeding episode
- Date and time of resolution of the bleeding episode

Study site personnel are qualified after they have undergone training during the qualification of the site.

All types of bleeds, including traumatic bleeds, will be recorded. Bleeding episodes should be organized by where they occur in addition to whether they occurred spontaneously or due to a traumatic event.

Bleeds occurring at the same anatomical location (e.g., right knee) with the same etiology (i.e., spontaneous versus injury) within 24 hours after onset of the first bleed will be considered a single bleed. Bleeding occurring at multiple locations related to the same injury (e.g., knee and ankle bleeds following a fall) will be counted as a single bleeding episode.

All efforts should be made to use rVWF (vonicog alfa) for treatment of bleeding episodes. If needed, the use of a VWF concentrate other than IP for the treatment of bleeding episodes will not disqualify the subject from further participation in the study.

11.2 Evaluation of ABR Before rVWF Prophylaxis and ABR Under rVWF Prophylactic Treatment

At screening, the subject's medical history will be recorded, including the number and location of all spontaneous and traumatic bleeding episodes within the past 12 months (up to 24 months if available). The maximum interval of bleed-free periods as well as trauma induced bleeding episodes will also be recorded (prospectively and retrospectively).

11.3 Number of Infusions and Total Weight Adjusted Consumption of rVWF and ADVATE and historical prophylaxis dosing and factor consumption during pdVWF prophylaxis treatment prior to enrollment

The number of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) (in case of bleeding episode treatment) infusions will be logged in the subject diary. Based on these entries the weight adjusted consumption will be calculated.

At the screening, historical pdVWF dosage and dosing frequency during 12 and up to 24 months of pdVWF prophylactic treatment prior to enrollment will be recorded for the pdVWF switch subjects in order to calculate the consumption of pdVWF.

11.4 Assessment of Efficacy for Treatment of Bleeding Episode

Investigators will be asked to assess and record hemostatic efficacy after resolution of each bleeding episode using the 4-scale rating system outlined in Table 4.

Table 4
Efficacy Rating Scale

Rating	Efficacy Rating Criterion	
	Minor and Moderate Bleeding Events	**Major Bleeding Events**
Excellent (=1)	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF containing coagulation factor containing product required	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF containing coagulation factor containing product required
Good (=2)	1-2 infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required	< 1.5 x infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required
Moderate (=3)	3 or more infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required	≥ 1.5 x infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required
None (=4)	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF containing coagulation factor containing product required	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF containing coagulation factor containing product required

11.5 Assessment of Efficacy for Treatment for Surgical Bleeding

For those undergoing surgery, the operating surgeon will be asked to assess and record actual versus predicated blood loss and intraoperative hemostatic efficacy immediately after surgery.

The investigator will be asked to assess and record an overall assessment of hemostatic efficacy 24 hours after the last perioperative rVWF (vonicog alfa) infusion or at day 14 post-operation, whichever occurs first, using the 4-scale rating system described in Table 5.

Table 5
Assessment of Hemostatic Efficacy

Rating	Overall Assessment of Hemostatic Efficacy 24 Hours After the Last Perioperative rVWF Infusion
Excellent (1)	Intra- and post-operative hemostasis achieved with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) was as good or better than that expected for the type of surgical procedure performed in a hemostatically normal subject
Good (2)	Intra- and post-operative hemostasis achieved with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) was probably as good as that expected for the type of surgical procedure performed in a hemostatically normal subject
Moderate (3)	Intra- and post-operative hemostasis with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) was clearly less than optimal for the type of procedure performed but was maintained without the need to change the rVWF (vonicog alfa) concentrate
None (4)	Subject experienced uncontrolled bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of rVWF (vonicog alfa) concentrate

11.6 rVWF Pharmacokinetics and Pharmacodynamics

PK will be assessed twice for all subjects.

For on-demand subjects, an initial PK assessment using a dose of 50 IU ± 5 IU/kg rVWF:RCo will be performed at the baseline visit, and 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 week 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 assay. 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 assessment using the subject's individualized dose will be performed shortly after reaching steady state, which is estimated to be reached for the majority of subjects after approximately 11 days from the 1st prophylactic dose. To fit any logistical requirements, samples for PK analysis can be taken after prophylaxis dose #5-6, and whenever possible, sample collections should be during the longer partial interval of the alternating irregular dosing intervals. For example, if a subject follows a dosing regimen as follows:

Date	Weekday	Dose number	Interval	Time from 1st 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 profile will be assessed at the end of the study, i.e. 12 month ± 2 week visit with a PK 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 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). If the dosing interval for a certain switch subject wouldn't allow for the full 11 post-infusion timepoints sample collection, 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 for an individual switch subject.

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

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

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, whether or not considered causally related to the IP.

12.1.1.1 Serious Adverse Event

An SAE is defined as an untoward medical occurrence that, at any dose, meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are (including but not limited to):
  - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
  - Reviewed and confirmed seroconversion for HIV, hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)

- Development of clinically significant neutralizing VWF antibodies
- Development of neutralizing antibodies to FVIII (titer ≥0.4 BU [by Nijmegen- modified Bethesda assay] or ≥0.6 BU [by Bethesda assay])
- Thromboembolic events (e.g., myocardial infarction, stroke, transient ischemic attack [TIA], deep vein thrombosis [DVT] or pulmonary embolism)
- Hypersensitivity reactions (e.g., anaphylaxis [for definition, refer to Section 12.6.2] and other immediate and delayed hypersensitivity reactions which may manifest with urticarial rash, pruritus, flushing, angioedema of the face, extremities, or laryngeal tissues [leading to throat tightness with stridor], wheezing, gastrointestinal symptoms, and/or hypotension)

Uncomplicated pregnancies, following maternal or paternal exposure to IP are not considered an AE/SAE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE and should be reported per SAE reporting guidelines provided in Section 12.1.2.3 (Safety Reporting).

12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any suspected adverse reaction to study treatment that is both serious and unexpected is considered a SUSAR.

The event(s) must meet all of the following:

- Suspected adverse reaction (which implies that there is reasonable evidence indicating a causal relationship between the event and the study treatment),
- Unexpected (per Reference Safety Information (RSI)/IB), and
- Serious

Once determined to meet the criteria for a SUSAR, the sponsor will ensure expedited SUSAR reporting is completed in line with the regulatory requirements in participating countries as outlined in the Safety Management Plan.

12.1.1.3 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet any of the seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) listed in Section 12.1.1.1.

12.1.1.4 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (e.g., IB, PI [prescribing information]). "Unexpected" also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.1.1.5 Preexisting Disease

Preexisting diseases that are present before entry in to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described as "worsening" of the pre-existing condition on the AE CRF.

12.1.2 Assessment of Adverse Events

For the purposes of this study, the following will not be considered as AEs and will not be included in the analysis of AEs.

- Bleeding episodes are part of the underlying disease and therefore are not AEs; they will be evaluated in the context of efficacy.
  - For non-serious bleeding episodes caused by an injury, the injury would not be reported as an AE, unless it resulted in a medical finding other than a bleeding episode (e.g., abrasion of skin). Therefore, any VWD-related bleeding event (e.g., epistaxis, gastrointestinal bleeding, musculo-skeletal bleeding, menorrhagia) that is non-serious will not be reported as an AE. However, the investigator may decide that the event is an AE if the event also would have occurred in a healthy individual under the same circumstances.
  - For serious bleeding episodes (bleeding SAEs): Bleeding events that meet seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) should be captured on the SAE eCRF and reported as an SAE to the Sponsor or designee (e.g., CRO) on an SAE Report form as described in Section 12.1.2.3 (Safety Reporting).
- Seroconversion after documented HAV/HBV vaccination prior to or during the study period.

Each AE from the first IP exposure to the study completion date will be described on the AE CRF using the term representing medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial verbatim expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2

For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable, action taken with regards to the study treatment (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution or until the subject's condition returns to the level at the baseline for pre-existing conditions.

If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the protocol-specified dosage (including underdosing /overdosing [<20 IU/kg rVWF:RCo or >100 rVWF:RCo], abuse, and withdrawal, treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after administration of IP will be reported on a Pregnancy Form and followed-up at 1 year post-delivery, if feasible.

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the SAE Form within 24 hours after awareness: no additional reporting on CRFs is necessary.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, e.g., assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs

- Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP, is not biologically plausible per mechanism of action of the IP, or has a much more likely alternative etiology).

- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of IP
  - An alternative etiology is equally or less likely compared to the potential relationship to the IP
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
    - Reappearance of a similar reaction upon re-administration (positive re-challenge)
    - Positive results in a drug sensitivity test (skin test, etc.)
    - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
  - Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within 5 days after IP infusion, the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

12.1.2.3 Safety Reporting

AEs and SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Section 20.2) and Section 12.1.2.

Adverse Events and SAEs are to be recorded on the AE page of the eCRF. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the IP, must be reported immediately (within 24 hours of the study center's first knowledge of the event). All SAEs must be reported in English via the Electronic Data Capture (EDC) system by completing the relevant eCRF page(s) and also by SAE Report Form via fax/email to Sponsor's Global Drug Safety (Baxalta GDS) department within 24 hours of becoming aware of the event for SAEs (for contacts, instructions, and additional details, refer to the SAER form).

Within 24 hours of site awareness of a SAE (or Pregnancy) study sites will complete and send all SAE (or Pregnancy) reports to a dedicated:

Baxalta Global Drug Safety fax number: [redacted]

OR

email: [redacted]

The responsible Site Monitor will review the SAE (or Pregnancy) Reports for completeness, will reconcile the reports against the EDC database, and will follow-up with sites to obtain missing information and/or information requiring clarification. Any SAE associated with a pregnancy must be reported on the SAER Form.

For Follow-up Reports, the site shall use a new SAER form (marked as Follow-up) and the new information should be entered together with a brief narrative identifying the updated data.

An SAER should include the following minimum information:

1. Protocol Number (on all pages)
2. Subject identification number (on all pages) and demographics (gender, age at onset of event and/or date of birth)
3. Investigational product and treatment regimen (including date of the first dose of IP, date of the last dose of IP prior to the onset of the SAE)
4. Medical Term for Event (Diagnosis preferably)
5. Description of the SAE, including:
    - Date of onset
    - Causal relationship assessment by the Investigator
6. Seriousness criteria (e.g., death, life-threatening, hospitalization, medically significant, or other criterion)
7. Name, address, fax number, email, and telephone number of the reporter/Investigator

Post-trial SAE Reporting: In compliance to EudraLex Volume 10 (Clinical trials guidelines, Chapter II: Safety Reporting from the European Commission), which references an EMA guidance (ICH Topic E 2 A - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting), clinical sites/the investigator should report to the Sponsor SAEs after a subject´s study completion. Study sites will be provided a Post-Trial SAER form to complete and report these post-study SAEs to the Sponsor within the 24 hours of their awareness. Site Monitor will instruct the site that any such Post-Trial SAEs should be reported on the study-specific Post-Trial SAER form if/when the site becomes aware of it. Such information will not be actively monitored by the sponsor after completion of the study.

These events shall be reported to Baxalta GDS who will process them in the same way as SAEs occurring during the study. Post-Trial SAEs do not need to be captured in the study EDC database if it is already locked. Irrespective if captured in the EDC database or not, such Post-Trial SAEs will become part of the GDS database. The monitor should remind the clinical site about the post-trial SAE reporting requirements during interim monitoring visits, upon each subject's study completion as well as during the close-out visit.

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of the clinical trial
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor.
In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committees (ECs) and relevant competent authority(s) are notified of the urgent measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (i.e., from the time of signed informed consent up to but not including the first IP exposure) will be described on the SAER. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE.** NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g. reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (e.g., potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) 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. The subject's medical history will also include documented history of on-demand or pdVWF prophylaxis treatment for at least the past 12 months and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 months (up to 24 months if available).

All medications taken and non-drug therapies received in the 2 weeks prior to study entry and all concomitant medications and non-drug therapies during study will be recorded on the CRFs.

Data on medical history, drug and non-drug therapy history of those subjects who transition from surgery rVWF (vonicog alfa) study will be used from the eCRF of the main studies, will be updated, if applicable, and transcribed into the respective eCRF of the prophy study.

12.6 Physical Examinations

At screening and subsequent study visits (as described in Section 10.3), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 12.1.1.5), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.6.1 Thromboembolic Events

There is a risk of occurrence of thrombotic events, particularly in patients with known clinical or laboratory risk factors for thrombosis including low ADAMTS13 levels. Therefore, patients at risk must be monitored for early signs of thrombosis during the study and prophylaxis measures against thromboembolism should be instituted according to current recommendations and standard of care. Additional diagnostic procedures are required according to each institution's standard of care which may consist of, but are not limited to the following:

- For DVT: Magnetic Resonance Imaging (MRI), compression ultrasound or impedance plethysmography.
- For pulmonary embolism: ECG, chest radiography, perfusion/scintiscan or MRI.
- For myocardial infarction: ECG, cardiac enzymes, echocardiography
- For stroke: diffusion-weighted magnetic resonance imaging or computed tomography, ABCD scoring, carotid imaging

Results of diagnostic procedures may be forwarded to the sponsor to be reviewed by an independent external expert panel, such as the DMC, if applicable.

12.6.2 Anaphylaxis

The diagnosis of anaphylaxis is highly likely when any of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g, generalized urticaria, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:
   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin or mucosal tissue (e.g., generalized urticaria, pruritus or flushing, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to a known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP

If a subject develops anaphylaxis in the course of the clinical study, this needs to be reported as SAE (Section 12.1.1.1). Additional blood will be drawn for Anti-VWF IgE antibody testing (Section 12.9.13).

12.7 Vital Signs

Vital signs will be assessed pre- and post-infusion at each visit, if not stated otherwise:

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

Vital signs (pulse rate, respiratory rate, and blood pressure) should be recorded within 30 min before and after IP administration. The assessment of vital signs per planned study visit is outlined in Supplement 20.2.

Vital sign values are to be recorded on the physical examination eCRF. For each vital sign value, the investigator will determine whether the value is considered an AE (see definition in Section 12.1). If assessed as an AE, the medical diagnosis (preferably), symptom, or sign, will be recorded on the AE eCRF. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE, should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.8 Electrocardiogram

A standard 12-lead ECG at rest will be performed at screening, at the 6 month follow-up visit and at the study termination visit and evaluated for medical significance by the investigator.

12.9 Clinical Laboratory Parameters

Refer to the Laboratory Manual for information on collection and processing of samples.

In general all laboratory tests will be performed at central laboratories, except the pregnancy and blood group test which will be performed at the local laboratory.

In addition, relevant critical safety laboratory tests for complete blood count (CBC), serum chemistry and/or coagulation parameters such as VWF and FVIII activity may also be performed in the local laboratory to ensure that results will be available immediately to the investigator. In principle, results from the central laboratory will be used for data analysis purposes. The assays performed in the central laboratories are specified in the Laboratory Manual. The investigator will supply the sponsor with a list of the normal ranges and units of measurement for the laboratory variables to be determined at the site. Laboratory values such as antibodies to other proteins are not required immediately and will be assessed later during the course of the study.

Any abnormal laboratory value that is considered clinically significant by the investigator based on a local laboratory test result (reference range and the units to be provided) should be confirmed by a central laboratory test result for which the sample is drawn/collected within 24 hours of the abnormal finding by the local laboratory.

12.9.1 rVWF Pharmacokinetics and Pharmacodynamics

Details on pharmacokinetic and pharmacodynamics assessments are provided in Section 11.6.

12.9.2 Hematology and Clinical Chemistry

The hematology panel will consist of CBC [hemoglobin, hematocrit, erythrocytes (ie, red blood cell count [RBC]; mean corpuscular volume [MCV], mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration [MCHC]), and leukocytes (i.e., white blood cell count [WBC])] with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.

The clinical chemistry panel will consist of sodium (Na), potassium (K), chloride (Cl), ALT, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase (AP), blood urea nitrogen (BUN), CR, and glucose (Glu).

Blood will be obtained for assessment of hematology and clinical chemistry parameters at screening, during PK-assessment prior to rVWF (vonicog alfa) IP infusion, after 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours post rVWF (vonicog alfa) IP infusion, at all follow-up visits as per schedule (refer to Supplement 20.3 Clinical Laboratory Assessments), i.e., 4 weeks ± 1 week, 8 weeks ± 1 week and every 3 months ± 2 weeks, and at study completion. Hematology and clinical chemistry assessments will be performed on Ethylenediaminetetraacetic acid (EDTA)-anticoagulated whole blood and serum, respectively, at the central laboratory.

12.9.3 Immunology

12.9.3.1 Antibodies to VWF and FVIII

All subjects will be tested for binding and neutralizing antibodies to VWF and FVIII at screening, at initial PK assessment, at each of the scheduled follow-up visits and at the study completion visit. Testing will be done prior to IP infusion and with at least a 72 hour wash out period since the last IP infusion. If there is any suspicion of inhibitor development (e.g. excessive bleeding) binding and neutralizing antibodies to VWF and FVIII may be tested at the discretion of the investigator.

12.9.3.2 Neutralizing and Total Binding Anti-VWF Antibodies

The assays to establish the presence of neutralizing and total binding anti-VWF antibodies have been established in the absence of international standards and with only limited numbers of positive controls. Therefore, caution is advised in interpreting positive results. In particular, any clinical association, changes in the natural history of the disease, effect of therapy, etc. needs to be taken into account for final judgment. The sponsor's Medical Director should be consulted for additional advice. As part of the AE follow-up, any sample testing positive needs to be confirmed after 2-4 weeks for central laboratory testing. Only confirmed neutralizing anti -VWF antibodies are considered inhibitors (see Section 12.9.3.4). These subjects need to be closely monitored and therapy adjusted accordingly.

12.9.3.3 Binding antibodies to VWF

The presence of total binding anti-VWF antibodies will be determined by an enzyme-linked immunosorbent assay (ELISA) employing polyclonal anti-human Immunoglobulin (Ig) antibodies (IgG, IgM and IgA). For this assay (ELISA), recombinant human VWF will be coated onto a microtiter plate, then incubated with dilutions of the positive control, the negative control or test sample. Antibodies against human VWF that are present in the samples bind to the coated antigen and will be detected with a horseradish peroxidase (HRP)-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a human monoclonal antibody specific for human VWF spiked into the negative control. The negative control for this assay is pooled normal human plasma.

Plasma samples are analyzed for binding antibodies against the specific antigen in two steps. First, the sample is screened for antibodies and the titer of binding antibodies is determined. Second, the specificity of positive antibody results is confirmed.[16]
In brief, all samples are serially diluted (initial dilution 1:20 and further diluted 1:2).

The titer endpoint, defined as the highest dilution that still gives a positive signal above cut off level, is determined in two independent duplicates. The cut off level is established based on background signal level of healthy plasma donors (n=160) and set to include 5% false positives to be as sensitive as possible (95% percentile). The ELISA assay is validated allowing an assay variability of ± 1 titer step. Therefore, differences ≤ 2 titers steps may be due to variability of the ELISA assay. Specificity has to be confirmed in a competition assay when a sample has a titer of 1:80 or higher in the screening assay. Based on the validation criteria samples tested in the screening assay at 1:20 or 1:40 cannot be confirmed in the competition assay. A positive screening value is confirmed if the difference between the titers determined for the subject sample (re-screen) and for the subject sample with pre-incubation (confirmation sample) is > 2 titer steps. Antibody titers of subject samples will only be reported as positive, if the results of the screening and confirmatory analysis fulfill these acceptance criteria. The titer to be reported is always the one determined in the original screening procedure (independent of the result of the re-screening in the confirmation procedure).

A more detailed test procedure will be supplied upon request or pro-actively if a sample tests positive. A treatment related increase of the binding anti-VWF antibodies is expected, if the titer increases by more than 2 titration steps. These subjects need to be closely monitored and therapy adjusted accordingly.

12.9.3.4 Neutralizing Antibodies to VWF

Three functional VWF assays, VWF:CB, VWF:RCo and VWF:FVIIIB assays, will be used to test for the presence of neutralizing anti-VWF antibodies. Neutralizing antibodies to VWF:RCo, VWF:CB and VWF:FVIIIB activities will be measured by assays based on the Bethesda assay established for quantitative analysis of FVIII inhibitors (Nijmegen modification of the Bethesda assay).[17] The amount of inhibitor is expressed as BU per mL. One BU is thereby defined as the amount of inhibitor that decreases the measured activity in the assays to 50% of that of the negative control samples. The assays were validated using human plasma samples from two type 3 VWD patients with low (1-2 BU/mL) and high (~10 BU/mL) titer inhibitors and plasma samples from non-human primates immunized with human rVWF (vonicog alfa) (>100 BU/mL).

If a subject has a measurable baseline level of VWF activity in the respective assay, it is taken into account in the calculation of the residual activity. However, if baseline levels are too high (>15% VWF:RCo), inhibitors may not be reliably detected.

To exclude false positive results, the detection limit for anti-VWF inhibitors was set to 1 BU/ml for all 3 assays. The rationale for this cut-off value is the relatively high CI of the underlying assays, making determinations at the end of the evaluation range of the Bethesda reference curve uncertain.[18] A more detailed test procedure may be requested to further characterize the anti-VWF inhibitors, if detected.

Only confirmed positive anti-VWF inhibitor test result will be reported and will be considered as a medically significant SAE.

12.9.3.5 Binding Antibodies to FVIII

Binding antibodies against FVIII will be analyzed using a proprietary enzyme immunoassay. The testing strategy will be as described for binding anti-VWF antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.3.6 Neutralizing Antibodies (Inhibitors) to FVIII

Neutralizing antibodies (inhibitors) to FVIII will be assessed by the Nijmegen modification of the Bethesda assay in a central laboratory. To verify a FVIII inhibitor, additional testing (such as tests for Lupus anticoagulants) may be initiated. Positive FVIII inhibitor tests will be defined as ≥ 0.4 BU by the Nijmegen-modified Bethesda assay that is confirmed by a second test performed on an independent sample obtained 2-4 weeks following the first test. Only confirmed positive FVIII inhibitor test result will be reported.

12.9.4 Antibodies to Other Proteins

Plasma will be assayed for the presence of antibodies against CHO protein (total Ig), murine IgG and human Furin (total Ig) using proprietary enzyme immunoassays. The testing strategy will be as described for binding anti- VWF antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.4.1 Anti-CHO Protein

Total Ig antibodies (IgG, IgA, IgM) against CHO protein will be analyzed. For this assay (ELISA), CHO protein derived from cultures of untransfected cells and propagated under the identical cell culture conditions used for ADVATE (rFVIII, octocog alfa) production will be coated onto a microtiter plate, then incubated with dilutions of the positive control, negative control or test sample. Antibodies against CHO protein that are present in the samples bind to the coated antigen and will be detected with a HRP-coupled goat anti-human antibody (secondary antibody).

The positive control for this assay will be a polyclonal goat anti-CHO protein antibody spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.4.2 Anti-Murine IgG

A commercially available ELISA (Medac, Hamburg, Germany) will be used to detect and to quantify IgG antibodies originating from human plasma that are directed against mouse-IgG (HAMA: human anti- mouse antibodies). Microtiter plates coated with mouse IgG will be incubated with dilutions of the standard, the positive control, the negative control or the test sample. Antibodies against mouse IgG that are present in the samples bind to the coated antigen and form a bridge to a peroxidase coupled mouse IgG antibody that will be used for detection (bridging format of the ELISA assay).
The positive control for this assay will be a polyclonal goat anti-murine IgG spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.4.3 Antibodies to Human Furin

Total Ig antibodies (IgG, IgA, IgM) against human Furin will be analyzed. For this assay (ELISA), recombinant human Furin will be coated onto a microtiter plate, then incubated with dilutions of the positive control, the negative control or test sample. Antibodies against human Furin that are present in the samples bind to the coated antigen and will be detected with a HRP-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a human monoclonal antibody specific for human Furin spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.5 Viral Serology

The following viral seromarkers will be assessed at screening:

- HIV: anti-HIV 1, HIV 2
- HAV: anti-HAV (IgG and immunoglobulin M [IgM])
- HBV: Hepatitis B surface antigen (HbsAg), anti-Hepatitis B (HB) core, anti-HBs
- HCV: anti-HCV ELISA
- Parvovirus B19: anti-B19V (IgG and IgM)

Virus serology will be established during the screening period. The relevant confirmatory Polymerase Chain Reaction (PCR) testing may be performed from appropriate left-over samples as needed.

12.9.6 Urinalysis (Dipstick)

The urinalysis will include assessments for erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite and pH and will be performed at the central laboratory.

12.9.7 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. The pregnancy test may need to be repeated during the course of study in countries where mandated by national law.

12.9.8 VWD Mutational Analysis, Multimer Analysis and Human Leukocyte Antigen Genotyping

A cell pellet (buffy coat and erythrocytes) will be retained at the screening visit for VWD gene mutational analysis, VWF multimer analysis and HLA genotype determination if the information is not already available in the subject's medical history. Results from multimer analysis (see Section 12.9.10.1) may contribute to VWD gene mutational analysis. The genetic testing will be done, when the subject consents to the genetic testing.

12.9.9 Blood Group Analysis

The blood group needs to be determined during the screening period. If the information is not already available in the subject's medical history, it has to be determined at the local lab.

12.9.10 Additional Laboratory Testing in Case of Thromboembolic Events

rVWF (vonicog alfa) contains ULMW multimers because of a lack of exposure to endogenous VWF protease (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) during the manufacturing process. In vitro and in vivo cleavage of these ultralarge molecular fractions by ADAMTS13 and generation of characteristic satellite bands has been extensively demonstrated during nonclinical and clinical development. Nevertheless, the potential elevated risk of thrombosis and/or other thromboembolic complications due to the administration of ultra large molecular VWF multimers in subjects with normal levels of VWF cannot be completely excluded. Therefore VWF multimer analysis will not only be performed routinely at screening but in case of thromboembolic events, both VWF multimer analysis as well as ADAMTS13 activity will be determined to assess any relatedness of these occurrences with IP treatment.

12.9.10.1 VWF Multimer Analysis

The VWF multimer pattern will be assessed using low-resolution sodium dodecyl sulfate (SDS)–agarose gel electrophoresis. High-resolution SDS–agarose gel electrophoresis, with agarose concentrations >1.5%, will be used to determine the satellite band structure of VWF. These analyses will employ Western blot with luminescence video imaging.

12.9.10.2 ADAMTS13 Activity

VWF73 was identified as the 73 amino acid minimal region of the VWF A2 domain required for ADAMTS13 cleavage. The cleavage of this substrate will be detected by a commercially available ELISA-based Chromogenic assay (Technoclone Austria): Cleavage of immobilized VWF73 substrate is detected by a HRP-labeled antibody directed against the cleavage site of VWF73. The amount of bound antibody, which is the function of the ADAMTS13 cleavage is detected by a chromogenic substrate.

12.9.11 Soluble P-Selectin (sP-Selectin)

sP-selectin is a cell adhesion molecule (CAM) found in granules in endothelial cells (cells lining blood vessels) and activated platelets. Data for an association between the sP-selectin concentration, TTP and venous thromboembolism (VTE) are limited and the predictive value has not yet established. A commercial ELISA assay will be employed as an exploratory test. sP-selectin will be determined at the Screening visit and used as indicator for an increased thrombotic risk.

12.9.12 D-Dimer

D-dimer will be used as a marker for DVT and disseminated intravascular coagulation (DIC). While a negative result practically rules out thrombosis, a positive result can indicate thrombosis but does not rule out other potential etiologies, including a recent hemorrhage. Its main use, therefore, is to exclude thromboembolic disease where the probability is low. D-Dimer will be measured at the Screening visit and used as indicator for an increased thrombotic risk.

12.9.13 Additional Laboratory Testing in Case of Severe Hypersensitivity Reactions

If a subject develops a severe hypersensitivity reaction in the course of the clinical study, additional blood will be drawn for anti-VWF IgE antibody testing. The presence of anti-VWF IgE will be determined by using the ImmunoCAP®, a VWF-specific IgE blood test (Thermo Scientific). The basis of the ImmunoCAP® technology is a cellulose polymer as solid phase in a plastic capsule providing a large surface for protein binding. rVWF (vonicog alfa) as antigen is covalently coupled to the cellulose polymer.

Detection of specific anti-VWF IgE bound to the antigen will be accomplished by a secondary enzyme-labeled anti-human IgE antibody. Testing for binding anti-human VWF IgE antibodies will be done with 0.5 mL plasma. Antibody containing samples will be identified and quantified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.14 Assessment of Laboratory Values

12.9.14.1 Assessment of Abnormal Laboratory Values

For VWF and FVIII laboratory assessments no evaluation of clinical significance is necessary.

Each other laboratory value (except results to determine genetics of the underlying VWD disease and blood group) has to be assessed by the investigator and the assessment will be recorded on the eCRF. The investigator will determine for each abnormal laboratory value whether the value is considered clinically significant or not and provide the reference range including the units. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 12.1) and record the sign, symptom, or medical diagnosis on the AE CRF, is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.5), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, i.e. because it is due to a preexisting disease, due to a lab error, due to variation or due to another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator. Any abnormal laboratory value that is considered clinically significant by the investigator based on a local laboratory test result (reference range and the units to be provided) should be confirmed by a central laboratory test result for which the sample is drawn/collected within 24 hours of the abnormal finding by the local laboratory.

Any seroconversion result for HIV, HAV, hepatitis B virus (HBV), HCV, HEV, or B19V shall be re-tested.

12.10 [redacted]

12.10.1 [redacted]

12.10.2 [redacted]

13. STATISTICS

13.1 Sample Size and Power Calculations

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 cohort (OD and switch). A total of at least 5 type 3 VWD subjects will be followed for 12 months. 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).[1]

13.2 Datasets and Analysis Cohorts

13.2.1 Safety Analysis Set

The Safety Analysis Set will be composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

13.2.2 Full Analysis Dataset

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

13.2.3 Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set will be composed of subjects who are at least 70% compliant regarding the number of scheduled prophylactic infusions (as measured by the ratio of actual number of infusions to planned number of infusions). Only subjects who met all study entry criteria and who had no major protocol violations that might impact primary efficacy assessments will be included in the PP analysis set.

13.2.4 PK Full Analysis Set

The Pharmacokinetic Full Analysis Set (PKFAS) will be composed of all subjects who received the PK infusion and who provided acceptable data for PK and PD analysis. Acceptable PK/PD data will be defined in the Statistical Analysis Plan.

13.2.5 PK Per Protocol Analysis Set

The Pharmacokinetic 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 affecting the PK period of the study as defined in the detailed Statistical Analysis Plan.

13.3 Handling of Missing, Unused, and Spurious Data

13.3.1 General

Statistical techniques will not be used to identify and exclude any observations as outliers from the analyses. If data are considered spurious, e.g. for lack of biological plausibility, it will be documented to include the reason for exclusion and the analyses from which the data were excluded.

13.3.2 Other

1. Regarding missing data in PK records:
    - Body weight: If a subject's weight is missing from the PK infusion record, the subject's last recorded weight will be used to calculate the weight-adjusted dose.
    - Concentration:
        - Baseline concentration levels reported as below the limit of quantification will be considered to be 0. Missing VWF baseline concentration levels (VWF: RCo, VWF: AG or VWF: CB) for Type 3 subjects will be set to 0.
    - Time:
        - If start time of infusion is missing (but stop time is available) and actual collection time is available, then stop time of infusion will be taken for further calculation (i.e. time difference between actual end date/time of infusion and date/time blood sample drawn).
        - If actual collection date/time is missing and planned collection date/time is missing, then this PK time point will be taken out from the PK analysis (i.e. no data entry for this time point).
        - For all other scenarios, the planned collection date/time will be taken for further calculation.
2. Regarding missing data in AE records:
    - Handling of unknown causality assessment:
        - If a subject experiences an AE with a missing causality assessment, the relationship of the AE will be counted as "related."

- Handling of unknown severity grades:
  - If a subject experiences more than one AE categorized under the same preferred term, 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.

13.4 Methods of Analysis

The study success criteria are the objectives as stated in Section 7. “Treatment success” was defined as the extent of control of bleeding episodes achieved during this study.

13.4.1 Primary Outcome Measure

The primary outcome measure is ABR for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa). No formal statistical hypothesis test is planned for the analysis. The primary efficacy analysis will be based on the FAS and will be summarized by the two cohorts: on-demand and switch subjects. As a supportive analysis, the same analysis will also be carried out on the PP analysis set.

The spontaneous ABR while treated with rVWF (vonicog alfa) for each cohort will be estimated using a negative binomial regression. The prior ABR will be based on historical data collected from each enrolled subject.

The two ABRs (prior to prophylaxis treatment and while on prophylaxis) for each cohort will be compared within each subject using a generalized linear mixed-effects model (GLMM) (with a logarithmic link function, the default for the negative binomial distribution), accounting for the fixed effect of the two treatments. The follow-up time (in years) will be specified as an offset. The ratio of ABR while in the study to historical ABR will be estimated and reported together with the 95% confidence interval for each of the two cohorts.

The difference in on-study ABR relative to historical ABR will be also summarized descriptively.

13.4.2 Secondary Outcome Measures

In general, data for secondary efficacy analysis will be summarized by the two cohorts: on-demand and switch subjects and when applicable overall. Mean, standard deviation, median, range, quartiles will be calculated for continuous endpoints. Proportions, will be calculated for categorical endpoints. Confidence intervals at the two-sided 95% level will be provided when appropriate.

13.4.2.1 Additional Efficacy of Prophylaxis Treatment with rVWF

The number and proportion of on-demand subjects with ABR percent reduction success (i.e.≥ 25%) will be calculated together with a two-sided, 95% CI for the proportion.

The number and proportion of pdVWF switch subjects ABR preservation success will be reported together with the corresponding 95% two-sided CIs for the proportion.

The number and proportion of subjects with categorized spontaneous ABR (i.e. 0, 1-2, 3-5, more than 5 bleeds) will be reported descriptively.

Summary statistics for the total number of infusions, as well as average number of infusions per week will be provided. The total weight adjusted consumption of rVWF (vonicog alfa) during prophylactic treatment will be provided. If applicable, historical data on consumption of pdVWF prior to the study will be summarized as well.

The change in spontaneous ABR from the historical rate to that during the rVWF (vonicog alfa) prophylaxis period will be summarized by location of bleeding (GI, epistaxis, joint bleeding, menorrhagia, oral and other mucosa, muscle and soft tissue, etc.).

13.4.2.2 Pharmacokinetic and Pharmacodynamic Analysis

All PK and PD analyses will use the actual sampling times, not nominal times specified in the protocol, wherever possible. Actual sampling times will be defined as time from the start of infusion to the blood sample collection time. A deviation from the protocol-specified blood sample 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 results were biologically implausible will be eliminated from the analysis.

If any concentration data are considered spurious (e.g. lack of biological plausibility), the reason for exclusion from the analysis and the analysis from which the data point was excluded will be documented.

Details of calculation of PK and PD parameters and corresponding analysis will be given in the statistical analysis plan.

The following PK parameters, based on the initial PK assessment after a washout for on-demand subjects, will be listed and summarized descriptively for VWF:RCo, VWF:Ag and VWF:CB: IR, $T_{1/2}$, MRT, $AUC_{0-\infty}$, $AUC_{0-tlast}$, C_{max}, T_{max}, V_{ss}, and CL. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity, based on the initial PK assessment after a washout for on-demand subjects will be assessed using C_{max}, T_{max}, and $AUC_{0-tlast}$. These PD parameters will be listed and summarized descriptively. PK parameters at steady state ($AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$) for the partial dosing interval will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study for VWF:RCo, VWF:Ag and VWF:CB and summarized descriptively for subjects with the same dosing regimens. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity will be assessed using $AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$. These PD parameters will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study and will be summarized descriptively for subjects with the same dosing regimens.

For the on-demand subjects, the PK of VWF:RCo will be analyzed using a population PK approach to characterize the single and multiple dose pharmacokinetics, including associated variability assessed at after washout and at end of study, respectively. The population PK analysis will be performed in a stepwise manner as outlined below.

1. Exploratory graphical analysis of VWF:RCo versus time data for identification of potential outliers and to inform the pharmacometric analysis.
2. Population PK model development for rVWF (vonicog alfa):
    a. Evaluate alternative structural and stochastic models to describe the typical and individual rVWF (vonicog alfa) profiles.
    b. Investigate and characterize the potential for a time dependency in CL of rVWF (vonicog alfa).
    c. Evaluate, and if necessary refine, the candidate final model

Details of this Population PK analysis will be given in a separate Population PK analysis plan.

For the switch subjects, differences in $AUC_{0\text{-}tau;ss}$, $C_{max;ss}$, and $C_{min;ss}$ assessess shortly after reaching steady state and assessed at the end of the study will be assessed by the ratio of geometric means and corresponding two-sided 95% confidence intervals for VWF:RCo, VWF:Ag,VWF:CB, and FVIII:C. These analyses will be performed using a linear mixed effects model with PK assessment (i.e. factor of two levels relating to the PK assessment shortly after reaching steady state and the PK assessment at end of study, respectively) as a fixed effect and subject as a random effect based on log-transformed PK parameters. 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.

Descriptive statistics will be used to summarize VWF:RCo, VWF:AG and VWF:CB and FVIII:C levels for each nominal time point on the PK curve.

For all subjects in the PKFAS activity/concentration vs. time curves will be prepared.

Formulas for PK parameters IR, $T_{1/2}$, MRT, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}tlast}$, C_{max}, T_{max}, V_{ss}, and CL, $AUC_{0\text{-}tau;ss}$, $C_{max;ss}$, $T_{max;ss}$,and $C_{min;ss}$ will be given in the statistical analysis plan and will be derived using non-compartmental methods in WinNonlin. Analysis of these parameters will be carried out on the PKFAS as well as on the PKPPAS.

13.4.2.3 Safety

Safety analysis will be performed overall and by the two cohorts: on-demand and switch subjects.

TEAEs are defined as AEs with start dates on or after the first exposure to IP. Summaries of AEs will be based on TEAEs unless otherwise indicated.

Occurrence of AEs and SAEs will be summarized descriptively, by system organ class and preferred term. The number and percentage of subjects who experienced AEs and SAEs, and the number of AEs and SAEs will be tabulated. In addition, the number of subjects who experienced AEs assessed as related to IP by the investigator, and the number of IP-related AEs will be tabulated. The number of patients with AEs by severity will be presented similarly.

A listing of all AEs will be presented by subject identifier, age, sex, preferred term and 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.

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 infusion, irrespective of being related or not related to treatment. Temporally associated AEs will be presented in summary tables.

AEs that occurred before first IP infusion will be listed separately.

Adverse events of special interest (AESI), such as hypersensitivity reactions and thromboembolic events, will be monitored throughout the study and statistical analysis will be conducted based on the search criteria (eg, standardised MedDRA queries [SMQ]) determined prior to database lock, and summarized.

For immunogenicity, frequency counts and percentages will be calculated for 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. Clinically significant changes relative to baseline in vital signs and clinical laboratory parameters (hematology, clinical chemistry) will be reported.

13.4.3 Exploratory Outcome Measures

[redacted]

13.4.3.1 [redacted]

[redacted]

13.4.3.2 [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

13.4.3.3 [redacted]

[redacted]

13.4.3.4 [redacted]

[redacted]

13.5 Planned Interim Analysis of the Study

No formal interim analysis is planned for this study.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Trial Agreement (CTA). If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the CTA.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable national and local regulatory requirements as described in the CTA. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

15.1.1 Investigator Report and Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the CTA. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the CTA. Auditing processes specific to the study will be described in the audit plan.

15.5 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. Also, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing whenever pdVWF is used instead of rVWF (vonicog alfa). The reason for this use must also be provided to the sponsor. The sponsor (Baxalta) will also ensure the responsible EC and relevant competent authority are notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.6 Laboratory and Reader Standardization

A central laboratory/reader will be used for all clinical assessments except for pregnancy testing and blood group test (refer to Section 12.9). Local laboratories are requested to provide their laboratory specifications of the individual tests that are also being tested locally.

16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the CTA.

16.2 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the CTA.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

16.3 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients and/or their legally authorized representative must sign an informed consent form before entering into the study according to applicable national and local regulatory requirements and ICH GCP. Before use, the informed consent form will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 16.2). The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable national and local regulatory requirements. Patients or their legally-authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent form, patients or their legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised informed consent form, which have been approved by the applicable EC and regulatory authorities, will be provided by the investigator to the subjects who consented to participate in the study

16.4 Data Monitoring Committee

This study will be monitored by aDMC. The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. 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 stop a trial if it finds toxicities or if treatment is proven to be not beneficial. Details will be defined in the DMC charter.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the CTA.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.7), records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, CRFs, SAERs, laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

If electronic format CRFs are provided by the sponsor, only authorized study site personnel will record or change data on the CRFs. If data is not entered on the CRFs during the study visit the data will be recorded on paper and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (e.g., ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the CTA.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the CTA.

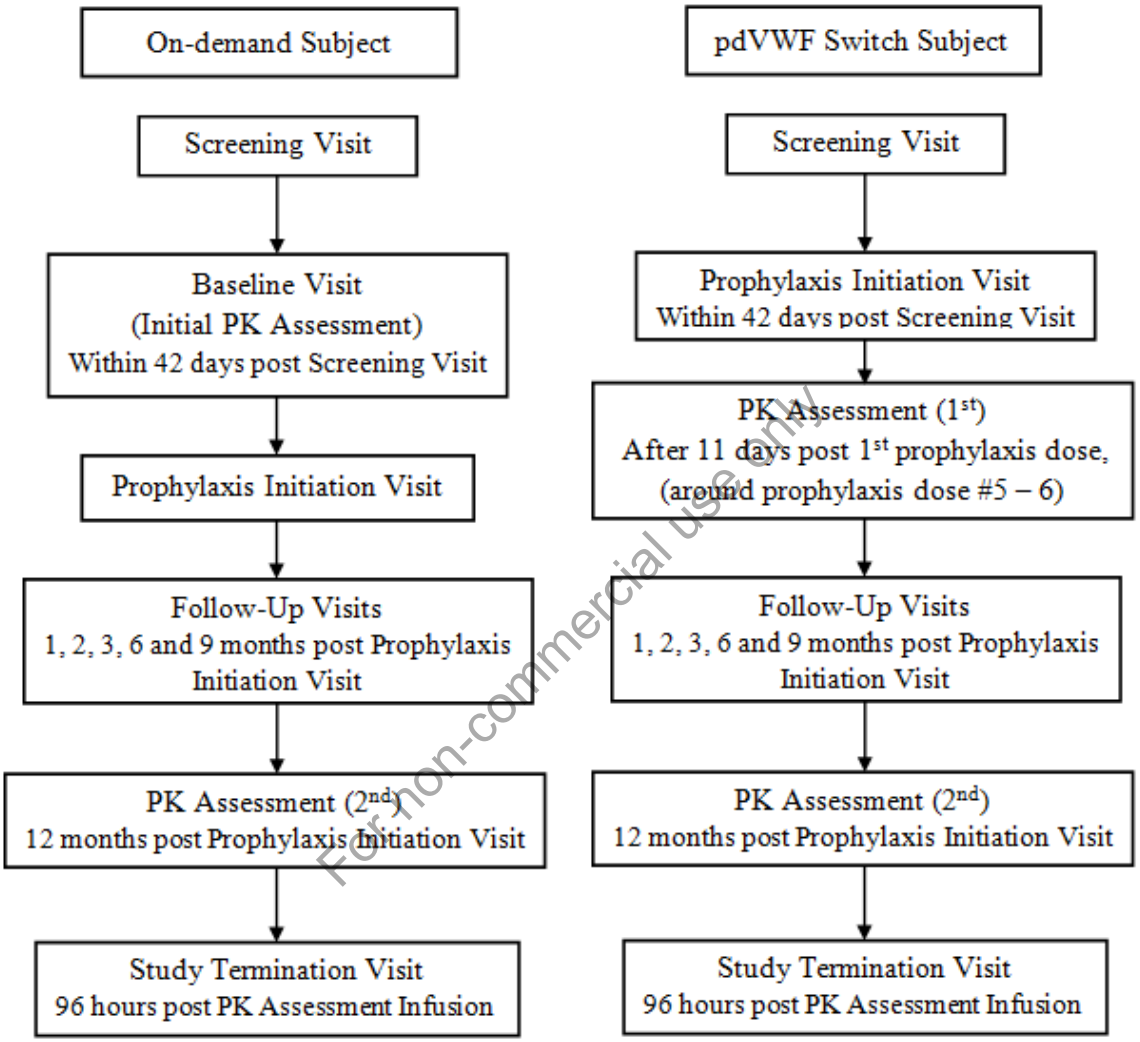
19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the CTA.

20. SUPPLEMENTS

20.1 Study Flow Chart

Figure 1
Study Design for Baxalta Clinical Study 071301



20.2 Schedule of Study Procedures and Assessments

Table 6a
Schedule of Study Procedures and Assessments for On-demand Subject

Procedures/ Assessments	Screening Visit	Baseline Visit (PK-assessment visit)			Prophylaxis Initiation Visit	Interval/Follow-Up Study Visits					PK Assessment at Study Completion			Termination Visit
		Pre-infusion[g]	Infusion	Post-infusion[g]		1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion[g]	Infusion	Post-infusion[g]	Conducted at the 96 hour postinfusion PK Assessment
											12 month ± 2 weeks			
Informed Consent [a]	X													
Eligibility Criteria	X													
Medical History[b]	X													
Concomitant Medications[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-drug Therapies[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X			X	X	X	X	X	X	X			X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Bleeding Episodes and Treatment and Hemostatic Efficacy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratories	X	X		X	X[h]	X	X	X	X	X	X		X	X
Vital Signs[d]	X	X		X	X	X	X	X	X	X	X		X	X
ECG	X								X					X
IP Treatment[e]			X		X	X	X	X	X	X		X		
IP Consumption / Treatment Compliance						X	X	X	X	X				
Subject Diary					X	X	X	X	X	X				
[redacted]	X[f]								X					X

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Continued

[a] Occurs at enrollment (before screening).
[b] Including documented history of on-demand treatment for the past 12 months (up to 24 months if available) and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 (up to 24) months.
[c] Including all medications and non- drug therapies taken in the 2 weeks prior to study entry and all the concomitant medications and non-drug therapies during the course of the study.
[d] Vital signs: height, weight, body temperature, pulse rate, respiratory rate, and blood pressure. Height is only required at the screening visit. The time points for pre- and post-infusion measurements are (weight is measured pre-infusion only): within 30 minutes before infusion start and 30 ± 15 minutes post-infusion.
[e] IP treatment after the prophylactic treatment initiation visit at the site will be continued as home-treatment if the subject qualifies; a wash-out period of at least 72 hours is required after the last IP infusion before the follow-up visit. IP infusion will be given at the study site after the blood sample for immunology testing and IR determination is drawn.
[f] Can be done either at the screening or the baseline visit.
[g] Time points for PK blood draws: 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 (the 96 hr sampling can be omitted if not allowed by the dosing interval).
[h] If a subject did not undergo PK assessment, laboratory assessments will be performed at this visit.

Table 6b
Schedule of Study Procedures and Assessments for pdVWF Switch Subject

Procedures/ Assessments	Screening Visit	Prophylaxis Initiation Visit	PK Assessment (at prophylaxis dose #5-6)			Interval/Follow-Up Study Visits					PK Assessment at Study Completion			Termination Visit
			Pre-infusion[g]	Infusion	Post-infusion[g]	1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion[g]	Infusion	Post-infusion[g]	Conducted at the 96 hour postinfusion PK Assessment
											12 month± 2 weeks			
Informed Consent [a]	X													
Eligibility Criteria	X													
Medical History[b]	X													
Concomitant Medications[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-drug Therapies[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X	X			X	X	X	X	X	X			X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Bleeding Episodes and Treatment and Hemostatic Efficacy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratories	X	X	X		X	X	X	X	X	X	X		X	X
Vital Signs[d]	X	X	X		X	X	X	X	X	X	X		X	X
ECG	X								X					X
IP Treatment[e]		X		X		X	X	X	X	X		X		
IP Consumption / Treatment Compliance						X	X	X	X	X				
Subject Diary		X				X	X	X	X	X				
[redacted]	X[f]								X					X

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Continued

[a] Occurs at enrollment (before screening).
[b] Including documented history of prophylaxis treatment for the past 12 months (up to 24 months if available) and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 (up to 24) months.
[c] Including all medications and non- drug therapies taken in the 2 weeks prior to study entry and all the concomitant medications and non-drug therapies during the course of the study.
[d] Vital signs: height, weight, body temperature, pulse rate, respiratory rate, and blood pressure. Height is only required at the screening visit. The time points for pre- and post-infusion measurements are (weight is measured pre-infusion only): within 30 minutes before infusion start and 30 ± 15 minutes post-infusion.
[e] IP treatment after the prophylactic treatment initiation visit at the site will be continued as home-treatment if the subject qualifies; a wash-out period of at least 72 hours is required after the last IP infusion before the follow-up visit. IP infusion will be given at the study site after the blood sample for immunology testing and IR determination is drawn.
[f] Can be done either at the screening or the prophylaxis initiation visit.
[g] Time points for PK blood draws: 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 (the 96 hr sampling can be omitted if not allowed by the dosing interval).

20.2.1 Summary Schedule of Visit Assesments for Surgical Bleeding

Table 7
Summary Schedule of Visit Assesments for Surgical Bleeding

Procedures/ Assessments	**Surgical procedure**				**Post-Operative Day 7 Visit (± 1 day)**	**Post-Operative Day 14 Visit (± 2 day)**
	Priming Dose Procedures (12-24 hours prior to surgery)	**Loading Dose Procedures (≤ 3 hours prior to surgery)**	**Intraoperative**	**Postoperative (day 1 → end of perioperative IP treatment)[a]**		
ECG						X
Physical examination[b]	X	X		X	X	X
Adverse events	X	X	X	X	X	X
Laboratories[c]	X	X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X
IP treatment: rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) or rVWF (vonicog alfa) only infusion	X	X as required	X as required	X as required	X as required	X as required
Concomitant medications and non-drug therapy	X	X	X	X	X	X
[redacted]						X
Hemostatic efficacy assessments[e]			X	X	X	X
Blood loss		X estimated	X actual	X	X[f]	X[f]
Treatment days estimate		X				

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Continued

[a] The assessments will be performed daily until perioperative IP treatment end (potentially multi-visits)
[b] Physical Examination: within 2 hours prior to IP infusion start
[c] For laboratory assessments, see Table 9
[d] Vital signs: within 30 minutes before infusion start and 30 ± 15 minutes post-infusion
[e] Completed immediately postsurgery by the operating surgeon 24 hours post last IP infusion or at Day 14 visit (whichever occurs first) by the investigator
[f] In case bleeding still ongoing

20.3 Clinical Laboratory Assessments

Table 8a
Clinical Laboratory Assessments for On-demand Subject

Procedures/ Assessments	Screening Visit	Baseline Visit (PK-assessment visit)			Prophylaxis Initiation Visit[k]	Interval/Follow-Up Study Visits					PK Assessment[m] at Study Completion			Termination Visit
		Pre-infusion	Infusion	Post-infusion		1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion	Infusion	Post-infusion	Conducted at the 96 hour postinfusion PK Assessment
											12 month± 2 weeks			
Hematology [a]	X	X		X	X	X	X	X	X	X	X		X	X
Clinical Chemistry[b]	X	X		X	X	X	X	X	X	X	X		X	X
Coagulation Panel/ PK assessment[c]	X	X		X	X	X	X	X	X	X	X		X	
Immunogenicity[d]	X	X			X[l]	X	X	X	X	X	X			X
Viral Serology[e]	X													
Urinalysis[f]	X													
VWD Gene Mutational Analysis / HLA genotype analysis and Analysis of VWF multimers[g]	X													
sP-selectin and D-dimer	X[h]													
Blood Group[i]	X													
Pregnancy Test[j]	X													

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Continued

[a] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. Hematology assessments during PK assessments will be determined prior to IP infusion and 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours thereafter. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

[b] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin. Clinical chemistry will be determined prior to IP infusion and after 24 ± 2 h, 48 ± 2 hours and 72 ± 2 hours during the PK assessments. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

[c] Coagulation panel/PK assessment (also refers to IR pre/post dose assessments at prophy initiation visit and each follow-up visit): PT, INR and aPTT (only for screening), VWF:RCo, VWF:Ag, VWF:CB, FVIII:C,; during the PK assessment at the baseline visit blood samples will be drawn 30 min prior PK infusion; once the PK infusion is completed 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 and VWF:RCo, VWF:CB, VWF:Ag, FVIII:C will be determined; for follow-up visits, IR samples will be drawn within 30 minutes pre-infusion and 30 ± 5 minutes post-infusion. During screening and in case of thromboembolic event VWF multimers and ADAMTS13 will be analyzed to judge on a possibly relatedness to UHMW fractions of the IP.

[d] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII –Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG . In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined. For on-demand subjects, a washout period of at least 72 hours after the last IP infusion is required before blood samples for immunogenicity assessments can be drawn.

[e] Viral Serology 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; HIV-1/HIV-2 Antibodies

[f] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH

[g] Not required if available in the subject's medical history; VWF multimers: additionally in case of thromboembolic events

[h] At screening and in case of thromboembolic events

[i] Blood group assessment major blood group (local laboratory) only if not available in the subject's medical history

[j] Serum pregnancy test (in females of child-bearing potential if no urine sample is available)

[k] The last post-infusion laboratory assessments coincide with the initiation visit for prophylactic treatment. After the blood samples are drawn for laboratory assessment for the 96 h post infusion PK assessment, the subject receives the first IP infusion for prophylactic treatment (prophylactic treatment initiation visit).

[l] Only needed for subjects without PK assessment prior to their first IP infusion in this study.

[m] A steady state full PK analysis will be performed at the end of the study. 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), the 96 hr sampling can be omitted if not allowed by the dosinig interval.

Table 8b
Clinical Laboratory Assessments for pdVWF Switch Subject

Procedures/ Assessments	Screening Visit	Prophylaxis Initiation Visit	PK Assessment[k] (at prophylaxis dose #5-6)			Interval/Follow-Up Study Visits					PK Assessment[k] at Study Completion			Termination Visit
			Pre-infusion	Infusion	Post-infusion	1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion	Infusion	Post-infusion	Conducted at the 96 hour postinfusion PK Assessment
											12 month± 2 weeks			
Hematology [a]	X	X	X		X	X	X	X	X	X	X		X	X
Clinical Chemistry[b]	X	X	X		X	X	X	X	X	X	X		X	X
Coagulation Panel/PK assessment[c]	X	X	X		X	X	X	X	X	X	X		X	
Immunogenicity[d]	X	X	X			X	X	X	X	X	X			X
Viral Serology[e]	X													
Urinalysis[f]	X													
VWD Gene Mutational Analysis / HLA genotype analysis and Analysis of VWF multimers[g]	X													
sP-selectin and D-dimer	X[h]													
Blood Group[i]	X													
Pregnancy Test[j]	X													

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[a] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. Hematology assessments during PK assessments will be determined prior to IP infusion and 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours thereafter. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

[b] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin. Clinical chemistry will be determined prior to IP infusion and after 24 ± 2 h, 48 ± 2 hours and 72 ± 2 hours during the PK assessments. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

[c] Coagulation panel/PK assessment (also refers to IR pre/post dose assessments at prophy initiation visit and each follow-up visit): PT, INR and aPTT (only for screening), VWF:RCo, VWF:Ag, VWF:CB, FVIII:C,; during the PK assessment blood samples will be drawn 30 min prior PK infusion; once the PK infusion is completed 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 and VWF:RCo, VWF:CB, VWF:Ag, FVIII:C will be determined; for follow-up visits, IR samples will be drawn within 30 minutes pre-infusion and 30 ± 5 minutes post-infusion. During screening and in case of thromboembolic event VWF multimers and ADAMTS13 will be analyzed to judge on a possibly relatedness to UHMW fractions of the IP.

[d] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII –Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG. In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined. For switch subjects, the wash out period may be reduced to the time interval between their pdVWF prophy infusions.

[e] Viral Serology 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; HIV-1/HIV-2 Antibodies

[f] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH

[g] Not required if available in the subject's medical history; VWF multimers: additionally in case of thromboembolic events

[h] At screening and in case of thromboembolic events

[i] Blood group assessment major blood group (local laboratory) only if not available in the subject's medical history

[j] Serum pregnancy test (in females of child-bearing potential if no urine sample is available)

[k] A full steady state PK analysis will be performed. 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) , the 96 hr sampling can be omitted if not allowed by the dosinig interval.

20.3.1 Laboratory Sampling for Surgical Bleeding

Table 9
Laboratory Sampling[a] for Surgical Bleeding

Procedures/ Assessments	**Surgical procedure**				**Post-Operative Day 7 Visit (± 1 day)**	**Post-Operative Day 14 Visit (± 2 day)**
	Priming Dose Procedures (12-24 hours prior to surgery)	**Loading Dose Procedures (≤ 3 hours prior to surgery)**	**Intraoperative**	**Postoperative (day 1 → end of perioperative IP treatment)[b]**		
Hematology[c]	X (w/o Differential)	X[d] (w/o Differential)		X (w/o Differential)	X	X
Clinical Chemistry[e]	X	X[d]			X	X
Coagulation panel[f]	X	X	X	X	X	X
VWF inhibitory and binding antibodies, antibodies to other proteins[g]	X	X	X if excessive or unexplainedbleeding	X	X	X
Urinalysis[h]					X	X
VWF Multimers[i]						
Anti VWF IgE antibody testing only in case of allergic reaction/ anaphylaxis						

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[a] Blood draws are within 3 hrs prior to infusion start, expect that for the priming dose blood draw is within 30 minutes prior to infusion start. For coagulation panel, an additional 30 ± 5 minutes post-infusion blood draw is needed.
[b] The assessments will be performed daily until perioperative IP treatment end (potentially multi-visits)
[c] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.
[d] Not required if sample already drawn at the time of the priming dose
[e] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin.
[f] Coagulation panel: VWF:RCo, VWF:Ag, FVIII:C PT INR and aPTT; in additiona to pre-infusion, 30 ± 5 minutes post infusion blood draw is needed.
[g] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII – Neutralizing and Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG. In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined.
[h] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH
[i] VWD multimers and ADAMTS13 during the study only in case of thrombotic events

20.4 Contraceptive Methods for Female Subjects of Childbearing Potential

In this study, subjects who are women of childbearing potential must agree to utilize a highly effective contraceptive measure throughout the course of the study and for 30 days after the last administration ofIP. In accordance with the Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials (version 2014-09-15)[ii], birth control methods which may be considered as highly effective include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable[iii]
- Intrauterine device (IUD)[iii]
- Intrauterine hormone-releasing system (IUS) [iii]
- Bilateral tubal occlusion[iii]
- Vasectomised partner(s)[iii]
- Sexual abstinence during the entire study period

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

[ii] Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf.

[iii] Contraception methods that are considered to have low user dependency.

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19. [redacted]

20. [redacted]

21. [redacted]

22. SUMMARY OF CHANGES

Protocol 071301: Local Amendment 7 (Germany): 2018 MAY 18

Replaces: Local Amendment 4 (Germany): 2017 AUG 04

In this section, changes from the previous local version of the protocol, dated 2017 AUG 04, are described and their rationale is given.

1. Throughout the document
   Description of Change:
   Minor grammatical and/or administrative changes and/or rewording have been made.
   Purpose for Change: To improve the readability and/or clarity of the protocol.

2. Throughout the document
   Description of Change:
   INN was added to rVWF and ADVATE by changing rVWF to rVWF (vonicog alfa) and changing ADVATE to ADVATE (rFVIII, octocog alfa).
   Purpose for Change: To add INN.

3. Section 2, Section 12.1.2
   Description of Change:
   Bleeding events that meet seriousness criteria should be reported on both SAE eCRF and SAE report form. Section 12.1.2.3 was added as a reference for SAE assessment.
   Purpose for Change: To provide further clarifications on SAE reporting.

4. Synopsis (Clinical condition(s)/indication(s)), Section 6.4, Section 13.1
   Description of Change:
   Original text:
   Subjects with severe von Willebrand disease (VWD) requiring prophylactic treatment with coagulation factor replacement.
   New text:
   Subjects with severe von Willebrand disease (VWD) **(baseline VWF:RCo <20 IU/dL)** requiring prophylactic treatment with coagulation factor replacement.
   Purpose for Change: To add definition of severe VWD.

5. Synopsis (Planned study period), Section 8.2
   Description of Change:
   The initiation/completion and duration of the study were updated per the new timeline.
   Purpose for Change: To reflect the new study timeline.

6. Synopsis (Study purpose, Study design), Section 7.1, Section 8.1
   Description of Change:
   Hypersensitivity was added for safety evaluation; PK and pharmacoecnomics evaluation was added.
   Purpose for Change: To provide further clarifications to the purpose of the study.

7. Synopsis (Primary objective), Section 7.2
   Description of Change:
   Original text:
   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 and to compare it to the subject's historical ABR **for spontaneous bleeding episodes during on-demand treatment**.
   New text:
   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 and to compare it to the subject's historical ABR for spontaneous bleeding episodes.
   Purpose for Change: To remove wording to accommodate pdVWF switch subject cohort, which is a new study cohort added in this amendment.

8. Synopsis (Secondary objectives), Section 7.3
   Description of Change:
   [redacted]. Additional wording was added to clarify the objectives.
   Purpose for Change: Remove some of the objectives ([redacted]) and add clarification.

9. Synopsis (Exploratory objectives, Exploratory outcome measures), Section 7.4, Section 8.3.3
Description of Change:
[redacted] and additional wording was added to clarify the assessments.
Purpose for Change: Clarification and adding additional objectives/assessments.

10. Synopsis (Study Design), Section 8.1
Description of Change:
Additional details about the study design were added for on-demand and the switch cohort.
Purpose for Change: To provide further clarification and to add study design for the switch cohort.

11. Synopsis (Primary outcome measure), Section 8.3.1
Description of Change:
Original text:
Prospectively recorded ABR for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF **and the subjects' historical ABR for spontaneous bleeding episodes during on-demand treatment**.
New text:
Annualized bleeding rate (ABR) for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa).
Purpose for Change: To remove the unnecessary text.

12. Synopsis (Secondary outcome measures), Section 8.3.2
Description of Change:
Rewording some of the exisiting secondary outcome measures (efficacy and safety) to provide clarification. New efficacy outcome measures were added to further access the efficacy of prophylaxis for switch subjects. Clinically significant changes in vital signs and clinical laboratory parameters were added as one additional safety measure. New steady-state PK parameters were added. PD parameters were added. [redacted]
Purpose for Change: To provide further clarifications and to add new outcome measures for switch subjects. And to remove some of the outcome measures ([redacted])

13. Synopsis (Investigational product(s), dose and mode of administration)
Description of Change:
Prophylaxis dosing guidelines were added for the pdVWF switch subjects.
Purpose for Change: To add dosing guide for the switch subjects.

14. Synopsis (Targeted accrual, sample size calculation), Section 6.4, Section 13.1
Description of Change:
Sample size was increased and targeted accrual of each cohort was added and a followup period of 12 months was added.
Purpose for Change: To update the sample to reflect the adding of switch cohort.

15. Synopsis (Inclusion criteria, Exclusion criteria), Section 9.1, Section 9.2
Description of Change:
Criteria for the switch subjects were added.
Criteria added to clarify no pre-planned surgery is allowed.
Purpose for Change: To update for the eligibility of switch subjects and to add some clarity.

16. Synopsis (Inclusion Criteria), Section 9.1
Description of Change:
Original text:
Subject is ≥18 years old at the time of screening and has a body mass index ≥18 but <30 kg/m^2.
New text:
Subject is ≥18 years old at the time of screening and has a body mass index ≥18 but ~~<30~~≤30 kg/m^2.
Purpose for Change: To update the BMI value from "18 - <30" to "18-≤30" range, in response to query received from regulatory authority in Germany only.

17. Synopsis (Planned statistical analysis), Section 13.4
Description of Change:
Changes were made throughout the section according to the updated outcome measures. Remove the planned analysis of exploratory outcome measure from synopsis to avoid redundance
Purpose for Change: To better test the updated outcome measures.

18. Section 5
Description of Change:
New abbreviations were added.
Purpose for Change: Clarification.

19. Section 6.5, Section 6.5.2, Section 6.5.2.4, Section 6.5.2.5
Description of Change:
Summary of recently completed clinical study 071101 was added as Section 6.5.2.4, the summary of 071401 was moved to Section 6.5.2.5.
Purpose for Change: To provide clinical study summary for study 071101.

20. Section 6.5.2.3
Description of Change:
To add wording about the basis of the dosing for the current study.
Purpose for Change: To provide clarification.

21. Section 6.6
Description of Change:
Original text:
He/she may benefit from a product that minimizes excessive FVIII administration.
New text:
He/she may benefit from a product that minimizes excessive FVIII administration **and thus allowing individualized dosing of VWF at optimal levels**.
Original text:
By using a recombinant product, the risk of **contamination with blood derived viruses or variant Creutzfeldt-Jakob Disease** associated with the use of products of human or animal origin has been **virtually** eliminated.
New text:
By using a recombinant product, the risk of **transmission of adventitious agents and other blood-borne pathogens** associated with the use of products of human or animal origin has been eliminated.
Purpose for Change: To provide accuracy and clarification.

22. Section 6.6
Description of Change:
Original text:
These benefits outweigh the following potential risks of rVWF.
New text:
These benefits outweigh the following **identified or** potential risks of rVWF
Purpose for Change: To provide accuracy since thromboembolic events has been upgraded to identified risk.

23. Section 8.5
Description of Change:
Updates were made based on safety considerations.
Purpose for Change: To avoid unnecessary study stop.

24. Section 8.6.3
Description of Change:
Wording was added to clarify that partial vials are not allowed to use.
Wording about mixing of two products was removed as it is not allowed any more.
Purpose for Change: To provide clarification on IP administration.

25. Section 8.6.4.1
Description of Change:
Details about PK assessment IP treatment were added for both on-demand and switch cohorts.
Purpose for Change: To provide more details and clarifications.

26. Section 8.6.4.2
Description of Change:
Prophylaxis initiation treatment was updated to be also applicable to the switch subjects and the dosing details were removed from this section (moved to Section 8.6.4.3).
Purpose for Change: To provide details to accommodate newly added switch cohort.

27. Section 8.6.4.3, Section 8.6.4.3.1, Section 8.6.4.3.2
Description of Change:
Detailed instructions of prophylaxis dosing and dosing adjustment were added to this section for both on-demand and pdVWF switch subjects. Home treatment rules were also made applicable to switch subjects, and made correction that the investigator is responsible for the home treatment procedures.
Purpose for Change: To provide details and clarifications to accommodate newly added switch cohort.

28. Section 8.6.4.4.1, Section 10.3.1
Description of Change:
Added the requirement of documentation the reason for the use of any non-IP product or therapy.
Purpose for Change: To ensure proper documentation of non-IP product use.

29. Section 8.6.4.4.2
Description of Change:
Added the wording about dose adjustment and the optional use of ADVATE.
Purpose for Change: To provide further clarification.

30. Section 8.6.4.5
Description of Change:
Sentence was added to clarify no pre-planned surgery is allowed.
Purpose for Change: To add some clarity.

31. Section 8.6.4.5.2
Description of Change:
Added description of priming dose for surgery.
Purpose for Change: To provide further clarification.

32. Section 8.6.4.5.3
Description of Change:
Added description of loading dose for surgery.
Purpose for Change: To provide further clarification.

33. Section 8.6.4.6, Section 12.6.1
Description of Change:
Added the details about prophylaxis measures against thromboembolism.
Purpose for Change: To ensure safety monitoring of thromboembolic events.

34. Section 8.6.5
Description of Change:
Added the wording about the requirement to monitor temperature excursions at the subject's home.
Purpose for Change: To ensure IP is stored as specified in the Pharmacy Manual.

35. Section 9.4
Description of Change:
Original text:
Subjects who develop a neutralizing inhibitor to rVWF and/or ADVATE (biological assays).
New text:
Subjects who develop a neutralizing inhibitor to rVWF and/or ADVATE (biological assays) **that results in significant clinical effect, including but not limited to increasing the weekly dose of rVWF by ≥ 50%.**
Purpose for Change: To provide more clarifications.

36. Section 9.4
Description of Change:
One more discontinuation criteria was added.
Purpose for Change: To avoid the continue of non-compliance subjects.

37. Section 10.3.1
Description of Change:
Added the wording to clarify the wash-out period of the screening visit and the timing of the subsequent visit for switch subjects.
Purpose for Change: To clarify for switch subjects.

38. Section 10.3.2
Description of Change:
Wording was added to specify this visit only applicable to on-demand cohort.
Purpose for Change: To provide clarification.

39. Section 10.3.3
Description of Change:
Wording was added to specify the timing of this visit for the switch cohort.
Purpose for Change: To provide clarification.

40. Section 10.3.4
Description of Change:
The initial steady-state PK assessment that only applicable to the switch subjects was specified in this section.
Purpose for Change: To accommodate PK assessment of switch subjects.

41. Section 10.3.5, Section 10.3.6, Section 10.3.7, Section 10.3.8, Section 10.3.9
Description of Change:
The original sections from 10.3.4 – 10.3.8 became 10.3.5 – 10.3.9 due to the insertion of new Section 10.3.4.
Purpose for Change: To accommodate the insertion of new Section 10.3.4.

42. Section 10.3.7
Description of Change:
The value of prophylaxis dose was removed since it was not correct for switch patients. The different wash-out period for switch subjects was specified.
Purpose for Change: To make corrections and to make clarifications for switch subjects.

43. Section 10.3.9
Description of Change:
Wording was added to clarify that the EOS PK assessment also applicabe for switch subjects and the wash-out requirement for switch subjects was added. The details about PK parameters were removed (specified in other sections).
Purpose for Change: To provide clarifications for switch subjects.

44. Section 10.4
Description of Change:
Added more clarification about the use of Antifibrinolytics.
Purpose for Change: To provide further clarifications.

45. Section 10.5
Description of Change:
Added more details about what would be recorded in the diary.
Purpose for Change: To provide further clarifications.

46. Section 11.2, Section 12.5
Description of Change:
Specified the need of location for historical bleeds records. Clarified that it is good to have upto 24 months of historical records if available.
Purpose for Change: To provide further clarifications.

47. Section 11.3
Description of Change:
Added more details about what would be needed for switch subjects as the historical factor dosing and consumption records.
Purpose for Change: To provide further clarifications.

48. Section 11.5
Description of Change:
Clarify the assessment of overall assessment of hemostatic efficacy.
Purpose for Change: To provide clarifications.

49. Section 11.6
Description of Change:
Section title was updated to add PD assessment.
PK/PD assessment details including schedule, dosing, parameters, etc.
Purpose for Change: To provide instruction/protocol for PK/PD assessment.

50. Section 12.1.1.1
Description of Change:
More details about hypersensitivity reactions were specified. SAE reporting reference was added.
Purpose for Change: To provide further clarification.

51. Section 12.1.1.2
Description of Change:
More clarifications about SUSAR were added.
Purpose for Change: To provide further clarification.

52. Section 12.1.1.3
Description of Change:
More details about criteria of serious AE were added.
Purpose for Change: To provide further clarification.

53. Section 12.1.2
Description of Change:
Some wording of clarification was added for assessment of AE.
Purpose for Change: To provide further clarification.

54. Section 12.1.2.2
Description of Change:
Original text:
Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).
New text:
Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP**, is not biologically plausible per mechanism of action of the IP,** or has a much more likely alternative etiology).
Purpose for Change: To provide more clarifications.

55. Section 12.1.2.3
Description of Change:
More details about hypersensitivity reactions were specified. SAE reporting reference was added.
Purpose for Change: To provide further clarification.

56. Section 12.7
Description of Change:
Added clarification that height is only assessed on screening visit.
Purpose for Change: To provide further clarification.

57. Section 12.9, Section 12.9.14.1
Description of Change:
"Abnormal laboratory values deemed clinically significant by the investigator are to be recorded as AEs (see Section 12.1.2)." was removed due to inaccuracy.
New Text added: "Any abnormal laboratory value that is considered clinically significant by the investigator based on a local laboratory test result (reference range and the units to be provided) should be confirmed by a central laboratory test result **for which the sample is drawn/collected** within 24 hours of the abnormal finding by the local laboratory".
Purpose for Change: To provide accuracy and further clarification.

58. Section 12.9.1
Description of Change:
Section title was updated to add PD assessment.
Text was removed, and refered to Section 11.6.
Purpose for Change: To avoid duplicated text.

59. Section 12.9.3.4
Description of Change:
Wording added to specify that only confirmed positive anti-VWF inhibitor test result will be reported and will be considered as a medically significant SAE.
Purpose for Change: To clarify.

60. Section 12.10.2
Description of Change:
[redacted]
Purpose for Change: [redacted]

61. Section 13.2.2
Description of Change:
Original text:
The Full Analysis Set (FAS) will be composed of all subjects **with available bleeding data gathered during** prophylaxis IP treatment.
New text:
The Full Analysis Set (FAS) will be composed of all subjects **who receive** prophylaxis IP treatment.
Purpose for Change: To re-define FAS.

62. Section 13.2.3
Description of Change:
Details were added on how to measure the compliance.
Purpose for Change: To add clarifications.

63. Section 13.2.4
Description of Change:
Wording added to clarify PK analysis set is also for PD analysis.
Purpose for Change: To add clarifications.

64. Section 13.4.2.2, Section 13.4.2.3
Description of Change:
[redacted]
Purpose for Change: [redacted]

65. Section 13.4.3.1, Section 13.4.3.2, Section 13.4.3.3 and Section 13.4.3.4
Description of Change:
[redacted]
Purpose for Change: [redacted]

66. Section 13.5
Description of Change:
Removed the interim analysis
Purpose for Change: No interim analysis is planned.

67. Section 15.5
Description of Change:
Additional instruction was provided to ensure the compliance by adding the text "Also, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing whenever pdVWF is used instead of rVWF. The reason for this use must also be provided to the sponsor".
Purpose for Change: To ensure compliance.

68. Section 20.1
Description of Change:
The study flow chart was updated to reflect the addition of switch cohort and to illustrate the study design for this new cohort.
Purpose for Change: To update the study design.

69. Section 20.2, Section 20.2.1

Description of Change:

Some clarifications were made to the tables and the footnotes, the original Table 6 was changed to 6a and specified just for on-demand subjects, Table 6b that is for switch subjects was added.

Purpose for Change: To provide schedule for the switch subjects and to provide clarifications for surgery procedure schedule.

70. Section 20.3, Section 20.3.1

Description of Change:

Some clarifications were made to the tables and the footnotes, the original Table 8 was changed to 8a and specified just for on-demand subjects, Table 8b that is for switch subjects was added.

Purpose for Change: To provide schedule for the switch subjects and to provide clarifications for surgery lab assessments.

INVESTIGATOR ACKNOWLEDGEMENT

RECOMBINANT VON WILLEBRAND FACTOR (rVWF)

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

CLINICAL TRIAL PHASE 3

LOCAL AMENDMENT 7 (GERMANY): 2018 MAY 18

Replaces: LOCAL AMENDMENT 4 (GERMANY): 2017 AUG 04

OTHER PROTOCOL ID(s)
NCT Number: NCT02973087
EudraCT Number: 2016-001478-14
IND NUMBER: 013657

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT

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Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
[redacted], MD
[redacted]
Global Clinical Development Operations
Baxalta Innovations GmbH

CLINICAL STUDY PROTOCOL

PRODUCT: Recombinant Von Willebrand Factor (rVWF, vonicog alfa)

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 SHORT TITLE: rVWF IN PROPHYLAXIS

PROTOCOL IDENTIFIER: 071301

CLINICAL TRIAL PHASE 3

LOCAL AMENDMENT 8 (CZECH REPUBLIC): 2018 MAY 18

Replaces:
LOCAL AMENDMENT 5 (Czech Republic): 2017 AUG 08

ALL VERSIONS:
Local (Czech Republic) Amendment 8: 2018 MAY 18
Local (Germany) Amendment 7: 2018 MAY 18
Amendment 6: 2018 MAR 12
Local (Czech Republic) Amendment 5: 2017 AUG 08
Local (Germany) Amendment 4: 2017 AUG 04
Amendment 3: 2017 AUG 03
Amendment 2: 2016 DEC 15
Amendment 1: 2016 APR 08
Original: 2014 FEB 19

OTHER ID(s)
NCT Number: NCT02973087
EudraCT Number: 2016-001478-14
IND NUMBER: 013657

Study Sponsor(s):

Baxalta US Inc.
300 Shire Way
Lexington, MA 02421,
UNITED STATES

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna,
AUSTRIA

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted]
Global Clinical Development Operations
Baxalta Innovations GmbH

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (e.g. investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) and suspected unexpected serious adverse events (SUSARs) to the ECs.

ALL SAEs, INCLUDING SUSARs, ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT.

Bleeding events that meet seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) should be reported on the SAE eCRF and SAE Report form as an SAE.

Drug Safety contact information:

Baxalta Global Drug Safety fax number: [redacted]

OR

email: [redacted]

For definitions and information on the assessment of these events, refer to the following:

- Adverse Events (AEs), Section 12.1
- SAEs, Section 12.1.1.1
- SUSARs, Section 12.1.1.2
- Assessment of AEs, Section 12.1.2
- Safety Reporting, Section 12.1.2.3

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	Recombinant von Willebrand factor (rVWF, vonicog alpha)
Name(s) of Active Ingredient(s)	Recombinant von Willebrand factor (rVWF, vonicog alpha)
CLINICAL CONDITION(S)/INDICATION(S)	
Subjects with severe von Willebrand disease (VWD) (baseline VWF: Ristocetin cofactor activity (VWF:RCo) <20 IU/dL) requiring prophylactic treatment with coagulation factor replacement	
PROTOCOL ID	071301
PROTOCOL TITLE	A prospective, phase 3, open-label, international multicenter study on efficacy and safety of prophylaxis with rVWF in severe von Willebrand disease
Short Title	rVWF in prophylaxis
STUDY PHASE	Phase 3
PLANNED STUDY PERIOD	
Initiation	2017 OCT
Primary Completion	2019 Q4
Study Completion	2019 Q4
Duration	27 months
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
The purpose of this phase 3 study is to investigate the efficacy and safety, including immunogenicity, thrombogenicity and hypersensitivity reactions, as well as pharmacokinetics (PK), [redacted] and [redacted] of prophylactic treatment with rVWF (vonicog alfa) in adult subjects with severe VWD.	
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.	
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 FVIII activity	

Exploratory Objectives	
[redacted]	
STUDY DESIGN	
Study Type/ Classification/ Discipline	Efficacy and Safety
Control Type	No control
Study Indication Type	Prophylaxis and treatment of bleeding episodes
Intervention model	Single-group
Blinding/Masking	Open-label
Study Design	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, [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 (pdVWF switch subjects) will receive prophylactic treatment with rVWF (vonicog alfa) for a 12-month period.
Planned Duration of Subject Participation	Approximately 15 months
Primary Outcome Measure	
Efficacy • Annualized bleeding rate (ABR) for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa)	
Secondary Outcome Measures	
Additional efficacy of prophylactic treatment with rVWF (vonicog alfa) • ABR percent reduction success for OD subjects defined as at least 25% reduction of ABR for spontaneous (not related to trauma) bleeding episodes during rVWF (vonicog alfa) prophylaxis relative to the subject's own historical ABR during on-demand treatment	

- ABR preservation success for pdVWF switch subjects 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 during prophylactic treatment with pdVWF
- Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 bleeding episodes during the 12-month 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
- Spontaneous ABR 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)

Safety

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

Pharmacokinetics (PK) and Pharmacodynamics (PD)

- PK parameters after a washout for on-demand 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 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 VWF:RCo, Von Willebrand factor antigen (VWF:Ag), Von Willebrand collagen binding activity (VWF:CB).
- PD parameters after a washout for on-demand subjects: C_{max}, T_{max}, and $AUC_{0-tlast}$ as measured in FVIII activity by the 1-stage clotting assay (FVIII:C).
- PK parameters at steady state for on-demand and switch subjects: area under the concentration versus time curve from 0 to end of the partial dosing interval ($AUC_{0-tau;ss}$), 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. PK parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.
- PD parameters at steady state for on-demand and switch subjects: $AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$ as measured in FVIII actvitiy by the 1-stage clotting assay (FVIII:C). PD parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.
- Time course of FVIII clotting activity (FVIII:C) levels.

Exploratory Outcome Measures	
[redacted]	
INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**Dosage form**: powder and solvent for solution for injection **Dosage frequency**: Prophylactic Treatment Subjects transitioning from on-demand treatment will receive twice weekly infusion with rVWF (vonicog alfa) at doses of 50 ± 10 IU/kg rVWF:RCo. Dosage may be individualized within this range based on: • available historical PK data • type and severity of bleeding episodes the subject has experienced in the past • monitoring of appropriate clinical and laboratory measures

	The starting dose can, after consultation with the Sponsor, be increased up to 80 U/kg if considered necessary to assure effective prophylaxis. Subjects switching from pdVWF prophylaxis treatment: the weekly dose (IU/kg) of rVWF (vonicog alfa) for each patient will be equivalent (± 10%) to the weekly VWF dose received during prophylactic treatment with pdVWF. The weekly dose should be divided into 2 infusions, 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. A once weekly dose regimen will be allowed after switch to rVWF (vonicog alfa) if the patient has been on a once weekly dose regimen with pdVWF. Dose and dose interval may, after consultation with the sponsor, be further individualized based on: • available historical PK data • type and severity of bleeding episodes the subject has experienced in the past • monitoring of appropriate clinical and laboratory measures <u>Treatment of Bleeding Episodes:</u> Dosage must be individualized based on the subject's weight, type and severity of bleeding episode and monitoring of appropriate clinical and laboratory measures. In general, an initial dose of 40-60 IU/kg VWF:RCo with or without 30-45 IU rFVIII [ADVATE, octocog alfa]/kg is recommended (rVWF:rFVIII ratio of 1.3:1: ± 0.2). In cases of major bleeding episodes, a dose of up to 80 IU/kg VWF:RCo may be infused. Subsequent doses, if necessary, will be administered with or without ADVATE (rFVIII, octocog alfa) to maintain VWF:RCo and FVIII levels for as long as deemed necessary by the investigator. **Mode of Administration:** intravenous
SUBJECT SELECTION	
Targeted Accrual	Approximately 22 adult subjects with severe VWD will be included to have ≥8 subjects in each cohort (OD and switch). A total of at least 5 type 3 VWD subjects will be followed for 12 months.
Number of Groups/ Arms/ Cohorts	Single-group

Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding:
    a. Type 1 (VWF:RCo <20 IU/dL) or,
    b. Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2M or,
    c. Type 3 (VWF:Ag ≤3 IU/dL).
2. Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.
3. For on-demand patient group, subject currently receiving on-demand treatment for whom prophylactic treatment is recommended by the investigator.
4. For pdVWF switch patient group, subject has been receiving prophylactic treatment of pdVWF products for no less than 12 months prior to screening.
5. For on-demand patient group, subject has ≥3 documented spontaneous bleeds (not including menorrhagia) requiring VWF treatment during the past 12 months.
6. Availability of records to reliably evaluate type, frequency and treatment of bleeding episodes during at least 12 months preceding enrollment. Up to 24 months of retrospective data should be collected if available. Availability of dosing and factor consumption during 12 months (up to 24 months) of treatment prior to enrollment is required for pdVWF switch subjects and is desired (but not a requirement) for on-demand subjects.
7. Subject is ≥18 years old at the time of screening and has a body mass index ≥17.5 but <40 kg/m^2.
8. If female of childbearing potential, subject presents with a negative blood/urine pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.
9. Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

Subjects who meet ANY of the following criteria are not eligible for this study:

1. The subject has been diagnosed with Type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD (e.g., qualitative and quantitative platelet disorders or elevated prothrombin time (PT)/international normalized ratio [INR] >1.4).
2. The subject is currently receiving prophylactic treatment with more than 5 infusions per week.
3. The subject is currently receiving prophylactic treatment with a weekly dose exceeding 240 IU/kg.
4. The subject has a history or presence of a VWF inhibitor at screening.
5. The subject has a history or presence of a FVIII inhibitor with a titer ≥0.4 Bethesda units (BU) (by Nijmegen modified Bethesda assay) or ≥0.6 BU (by Bethesda assay).
6. The subject has a known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins.
7. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
8. The subject has a medical history of a thromboembolic event.

9. The subject is human immunodeficiency virus (HIV) positive with an absolute Helper T cell (CD4) count <200/mm^3.
10. The subject has been diagnosed with significant liver disease per investigator's medical assessment of the subject's current condition or medical history or as evidenced by any of the following: serum alanine aminotransferase (ALT) greater than 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).
11. The subject has been diagnosed with renal disease, with a serum creatinine (CR) level ≥2.5 mg/dL.
12. The subject has a platelet count <100,000/mL at screening.
13. The subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to signing the informed consent.
14. The subject is pregnant or lactating at the time of enrollment.
15. Patient has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
16. The subject has participated in another clinical study involving another investigational product (IP) or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
17. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
18. The subject is scheduled for a surgical intervention.
19. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
20. The subject has a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
21. The subject is in prison or compulsory detention by regulatory and/or juridical order
22. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.

Delay criteria

1. If the subject presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) the screening visit will be postponed until the subject has recovered.

STATISTICAL ANALYSIS

Sample Size Calculation

Approximately 22 adult subjects with severe VWD will be included in the study. The aim is to have ≥8 subjects in each cohort (OD and switch). A total of at least five type 3 VWD subjects will be followed for 12 months. 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).[1]

Planned Statistical Analysis

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

The Safety Analysis Set will be composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

The Per-Protocol (PP) Analysis Set will be composed of subjects who are at least 70% compliant regarding the number of scheduled prophylactic infusions. Only subjects who meet all study entry criteria and who have no major protocol violations that might impact primary efficacy assessments will be included in the PP analysis set.

The Pharmacokinetic Full Analysis Set (PKFAS) will be composed of all subjects who received the PK infusion and who provided acceptable data for PK and PD analysis. Acceptable PK/PD data will be defined in the Statistical Analysis Plan.

Primary Outcome Measure:

No formal statistical hypothesis test is planned for the analysis. Spontaneous ABR while treated with rVWF (vonicog alfa) for each cohort, on demand and switch subjects, will be estimated using a negative binomial regression. The prior ABR for each cohort will be based on historical data collected from each enrolled subject. The two ABRs (observed on the study and historical) will be assessed 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 ABR ratio together with a two-sided, 95% confidence interval (CI) will be reported for each cohort.

The difference in on-study ABR relative to historical ABR will be summarized descriptively.

The primary efficacy analysis will be based on the FAS and will be summarized by the two cohorts: on-demand and switch subjects. As a supportive analysis, the same analysis will also be carried out on the PP analysis set.

Secondary Outcome Measures:

In general, data for secondary efficacy analysis will be summarized by the two cohorts: on-demand and switch subjects and when applicable overall. Mean, standard deviation, median, range, quartiles will be calculated for continuous endpoints. Proportions will be calculated for categorical endpoints. Confidence intervals at the 95% level will be provided when appropriate.

Additional efficacy of prophylactic treatment with rVWF (vonicog alfa):

The number and proportion of on-demand subjects with ABR percent reduction success (i.e. $\geq 25\%$) will be calculated together with a two-sided 95% CI for the proportion.

The number and proportion of pdVWF switch subjects with ABR preservation success will be reported together with the corresponding 95% two-sided CIs for the proportion.

The number and proportion of subjects with categorized spontaneous ABR (i.e. 0, 1-2, 3-5, more than 5 bleeds) will be reported descriptively.

Summary statistics for the total number of infusions, as well as average number of infusions per week will be provided. The total weight adjusted consumption of rVWF (vonicog alfa) during prophylactic treatment will be provided. If applicable, historical data on consumption of pdVWF prior to the study will be summarized as well.

The change in spontaneous ABR from the historical rate to that during the rVWF (vonicog alfa) prophylaxis period will be summarized by location of bleeding (GI, epistaxis, joint bleeding, menorrhagia, oral and other mucosa, muscle and soft tissue, etc.).

Pharmacokinetics (PK) and Pharmacodynamics (PD):

The following PK parameters, based on the initial PK assessment after a washout for on-demand subjects, will be listed and summarized descriptively for VWF:RCo, VWF:Ag and VWF:CB: IR, $T_{1/2}$, MRT, $AUC_{0-\infty}$, $AUC_{0-tlast}$, C_{max}, T_{max}, V_{ss}, and CL. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity (FVIII:C), based on the initial PK assessment after a washout for on-demand subjects will be assessed using C_{max}, T_{max}, and $AUC_{0-tlast}$. These PD parameters will be listed and summarized descriptively.

PK parameters at steady state ($AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$) for the partial dosing interval will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study for VWF:RCo, VWF:Ag and VWF:CB and summarized descriptively for subjects with the same dosing regimens. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity (FVIII:C) will be assessed using $AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$. These PD parameters will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study and will be summarized descriptively for subjects with the same dosing regimens.

For the on-demand subjects, the PK of VWF:RCo will be analyzed using a population PK approach to characterize the single and multiple dose pharmacokinetics, including associated variability, of VWF:RCo in the study population.

For the switch subjects, differences in $AUC_{0-tau;ss}$, $C_{max;ss}$, and $C_{min;ss}$ assessess shortly after reaching steady state and assessed at the end of the study will be assessed by ratio of geometric means and corresponding two-sided 95% confidence intervals for VWF:RCo, VWF:Ag, VWF:CB, and FVIII:C. 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.

Descriptive statistics will be used to summarize VWF:RCo, VWF:Ag, VWF:CB, and FVIII:C levels for each nominal time point on the PK curve. For all subjects activity/concentration vs. time curves will be prepared.

Safety:

Safety analysis will be performed overall and by the two cohorts: on-demand and switch subjects.

Treatment-emergent AEs (TEAEs) are defined as AEs with start dates on or after the first exposure to IP. Summaries of AEs will be based on TEAEs unless otherwise indicated.

Occurrence of AEs and serious AEs (SAEs) will be summarized descriptively, by system organ class and preferred term. The number and percentage of subjects who experienced AEs and SAEs, and the number of AEs and SAEs will be tabulated. In addition, the number of subjects who experienced AEs assessed as related to IP by the investigator, and the number of IP-related AEs will be tabulated. The number of patients with AEs by severity will be presented similarly.

A listing of all AEs will be presented by subject identifier, age, sex, preferred term and 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.

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 infusion, irrespective of being related or not related to treatment. Temporally associated AEs will be presented in summary tables.

Adverse events of special interest (AESI), such as hypersensitivity reactions and thromboembolic events, will be monitored throughout the study and statistical analysis will be conducted based on the search criteria (eg, standardized MedDRA queries [SMQ]) determined prior to database lock, and summarized.

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.

Clinically significant changes relative to baseline in vital signs and clinical laboratory parameters (hematology, clinical chemistry) will be reported.

4. TABLE OF CONTENTS

Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABR	Annualized bleeding rate
ADAMTS13	A Disintegrin And Metalloproteinase with a Thrombospondin type 1 motif, number 13
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the plasma concentration /time curve from time 0 to infinity
$AUC_{0-tau;ss}$	Area under the plasma concentration /time curve from time 0 to end of the partial dosing interval
$AUC_{0-tlast}$	Area under the plasma concentration /time curve from 0 to the last measurable concentration
aPTT	Activated partial thromboplastin time
B19V	Parvovirus B19
BP	Blood pressure
BU	Bethesda Unit
BUN	Blood urea nitrogen
BW	Body weight
CAM	Cell adhesion molecule
CBC	Complete blood count
CD4	Helper T cell
CHO	Chinese hamster ovary
CI	Confidence interval
Cl	Chloride
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max;ss}$	Maximum plasma concentration during the partial dosing interval at steady state
$C_{min;ss}$	Minimum plasma concentration during the partial dosing interval at steady state
CR	Creatinine
CTA	Clinical Trial Agreement
eCRF	Electronic case report form
DMC	Data monitoring committee
DIC	Disseminated intravascular coagulation

Abbreviation	Definition
DVT	Deep vein thrombosis
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
[redacted]	[redacted]
FAS	Full analysis set
FVIII	Factor VIII
FVIII:C	Factor VIII clotting activity
GCP	Good Clinical Practice
GI	Gastrointestinal
Glu	Glucose
HAMA	Human anti- mouse antibodies
HAV	Hepatitis A virus
HB	Hepatitis B
HBs	Hepatitis B surface
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
[redacted]	[redacted]
HRP	Horseradish peroxidase
IB	Investigator's brochure
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
INR	International normalized ratio
IP	Investigational product
IR	Incremental recovery
i.v.	Intravenous

Abbreviation	Definition
K	Potassium
k.o.	Knock out
LDH	Lactate Dehydrogenase
Na	Sodium
NMC	Non-medical complaint
NOAEL	No observed adverse effect level
MRI	Magnetic resonance imaging
MRT	Mean residence time
pdVWF	Plasma derived VWF product
pdVWF/FVIII	Plasma derived VWF product containing fractions of FVIII
PBAC	Pictorial Blood Assessment Chart
PCR	Polymerase Chain Reaction
PEF	Peak expiratory flow
PK	Pharmacokinetic
PKFAS	Pharmacokinetic Full Analysis Set
PKPPAS	Pharmacokinetic Per Protocol Analysis Set
PP	Per protocol
PT	Prothrombin time
Q1, Q3	Quartile
rFVIII	Recombinant factor VIII
rVWF	Recombinant von Willebrand factor
RBC	Red blood cell count
SAE	Serious adverse event
SAER	Serious adverse event report
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
[redacted]	[redacted]
SIC	Subject identification code
SMQ	Standardised MedDRA queries
sP-selectin	Soluble P-selectin
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Terminal phase half life
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack

Abbreviation	Definition
T_{max}	Minimum time to reach the maximum concentration
$T_{max;ss}$	Minimum time to reach the maximum concentration at steady state
TTP	Thrombotic thrombocytopenic purpura
ULMW	Ultra-large molecular weight
ULN	Upper limit of normal
V_{ss}	Volume of distribution at steady state
[redacted]	[redacted]
VTE	Venous thromboembolism
VWD	von Willebrand disease
VWF	Von Willebrand factor
VWF:Ag	Von Willebrand factor antigen
VWF:CB	Von Willebrand Factor collagen binding
VWF:RCo	Von Willebrand factor: Ristocetin cofactor activity
WBC	White blood cell

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

Baxalta US Inc. (hereafter referred to as Baxalta or sponsor) has developed a human recombinant von Willebrand Factor (rVWF, vonicog alfa), which is co-expressed with recombinant factor VIII (rFVIII) in a Chinese hamster ovary (CHO) cell line and separated during the subsequent downstream process. To address concerns regarding the risk of transmission of blood-borne pathogens that may be introduced by human plasma, no exogenously added raw materials of human or animal origin are employed in the cell culture, purification, or formulation of the final container product. The only proteins present in the final container product other than rVWF (vonicog alfa) are trace quantities of murine immunoglobulin (IgG, from the immunoaffinity purification), host cell (i.e., CHO) protein, rFurin (used to further process rVWF). rVWF (vonicog alfa) is intended for the treatment of von Willebrand disease (VWD).

rVWF (vonicog alfa) has been developed under the Baxalta internal code BAX111 and is used as investigational product (IP) in this study. rVWF (vonicog alfa) may be used with or without ADVATE (rFVIII, octocog alfa) for the treatment of bleeding episodes (see Section 8.6.4.4). See Section 8.6 for further information on the IPs and their usage in this study. A detailed description of rVWF (vonicog alfa) is also provided in the Investigator's Brochure (IB).

rVWF (vonicog alfa) was granted licensure in the United States in December 2015 under the brand name VONVENDI for the on-demand treatment and control of bleeding episodes in adults diagnosed with VWD; as of the date of this protocol VONVENDI is not yet available on the market.

6.2 Clinical Condition/Indication

Von Willebrand Factor (VWF) is a large multimeric glycoprotein with a molecular weight that varies from 500 to 20,000 kDa. VWF is normally found in plasma and produced in the alpha-granules of platelets and in endothelial cell organelles known as the Weibel-Palade bodies. VWF mediates platelet adhesion and aggregation at sites of vascular injury, one of the key functions in primary hemostasis. VWF also serves to stabilize coagulation factor VIII (FVIII), where FVIII is an essential cofactor of secondary hemostasis, which leads to fibrin clot formation.[2] Qualitative and/or quantitative deficiencies of VWF lead to a highly variable bleeding diathesis known as VWD, the most common of the hereditary coagulation factor deficiencies. Penetrance of VWD is highly variable, with only a small fraction of mildly affected patients displaying clinical symptoms or a family history of a bleeding diathesis.

The current biochemical-based classification distinguishes disorders arising from partial quantitative (type 1), qualitative (type 2), or virtually complete (type 3) deficiencies of VWF. Up to 70% of VWD patients are diagnosed with type 1 VWD, which may also be associated with minor functional defects in the molecule. In general, patients with type 1 VWD display mild clinical symptoms. Approximately 20 to 30% of VWD patients are diagnosed with type 2 VWD. Type 2 VWD is further divided into 4 subtypes (A, B, N, and M), reflecting distinct classes of functional abnormalities. These defects result in abnormal functional and/or multimeric distribution patterns that facilitate their diagnosis. The bleeding diathesis is usually moderate and primarily affects the mucosal tissues. Type 2N VWD patients are sometimes misdiagnosed as mild hemophilia A. Finally, approximately 1% percent of VWD patients exhibit a total or near total absence of VWF, which is classified as type 3 VWD. The incidence of type 3 VWD is estimated at 0.5-1.0 x 10^6. This type is also associated with a very low FVIII level (typically <5%) because the VWF carrier function for FVIII is lost. Replacement of VWF alone stabilizes endogenous FVIII, resulting in hemostatic levels within several hours post-infusion. Published results from studies of a plasma-derived VWF (pdVWF) concentrate demonstrated an increase of FVIII at an approximate rate of 5.8 ± 1 IU dL^{-1} h^{-1}.[3] Type 3 VWD patients display severe hemorrhagic symptoms with bleeding predominantly in mucosal tissues, muscle and joints. All VWD patients, particularly those with type 2 or type 3 VWD, are at an increased risk for life-threatening bleeding episodes.

6.3 The Role of Prophylaxis in the Management of VWD

The goals of long term prophylaxis in VWD are to maintain VWF and FVIII at sufficient levels to reduce the frequency and duration of bleeding episodes, the need for red blood cell transfusions, and the risk of complications, such as arthropathy.[4] In contrast to hemophilia, routine prophylaxis is not as established in VWD, although prophylaxis for patients with severe VWD was in use in Sweden already during the 1950s.[5] In those early days of VWD treatment, plasma FVIII concentrates containing VWF fractions were applied for replacement therapy, which then were followed by plasma derived VWF products containing fractions of FVIII (pdVWF/FVIII).

A Swedish cohort including 37 patients with type 3 VWD under prophylactic median treatment of 11 years (range 2 to 45 years) was retrospectively analyzed.[6,7] The doses used for prophylaxis, given once weekly for at least 45 weeks per year, were calculated based on 12 to 50 IU/kg body weight (BW) of FVIII clotting activity (FVIII:C) which approximately corresponded to 24-100 IU/kg von Willebrand factor: Ristocetin cofactor activity (VWF:RCo) considering that mainly Haemate with a known VWF:RCo/FVIII:C ratio of about 2 was used. An escalation of doses from 1 to 3 dose levels was allowed depending on the frequency and severity of bleeding episodes.

The results demonstrate that under long-term prophylaxis the number of bleeds could be reduced dramatically. Whereas the median value for bleeds per year was about 10 before prophylaxis this value could be reduced to less than 1 bleed per year during prophylaxis.

The benefit of prophylaxis for such indications was retrospectively also demonstrated in a cohort of Italian patients including type 3, 2A, 2M and type 1 patients. Prophylaxis was started after severe gastrointestinal or joint bleeding episodes and completely prevented bleeding episodes in 8 of these 11 patients and largely reduced the need of blood transfusions in the remaining 3. A regimen of 40 IU rVWF:RCo/kg was applied every other day or twice a week. A prospective study on prophylaxis, the PRO.WILL study, has been initiated in Italy.[8]

The results of a prospective study investigating the prophylaxis in children and young adults showed a significantly reduced bleeding frequency and bleeding score (3 vs. 0.07; 3 vs. 0. $p<0.001$) compared to the pre-prophylaxis values. The median dose was 40 (20-47) IU/kg VWF:RCo administered mainly twice weekly in 23 patients, 3 times a week in 7 patients and 4 times a week in 2 children.[9]

The VWD Prophylaxis Network initiated the VWD International Prophylaxis (VIP) trial to investigate the role of prophylaxis in patients with severe VWD including Type 1, 2, and 3. The dose of the factor replacement product was 50 IU /kgVWF:RCo. The frequency of the dose depended on the type of bleeding and could be increased from once weekly to twice weekly or 3 times per week. For the treatment of menorrhagia the dose of 50 IU/kg VWF:RCo was given on the first day of menses for 2 cycles. The frequency could be increased to Day 1 and 2 for 2 cycles or to Day 1, 2, and 3 of menses.

The study contains both retrospective and prospective study components. Results from the retrospective study component were published, including 61 subjects on prophylactic regimen in the past 6 months prior to enrollment or subjects with a history of prophylaxis over at least 6 month.[10] Differences in annualized bleeding rates (ABR) within individuals (during prophylaxis – before prophylaxis) were significant for those with primary indications of epistaxis ($P = 0.0005$), joint bleeding ($P = 0.002$) and GI bleeding ($P = 0.001$). The difference in the group whose primary indication for treatment was abnormally heavy bleeding at menstruation ($n = 4$) was not significant ($P = 0.25$). The reduction of mucosal bleeding likely not only dependents on normal circulating levels of active VWF, but also on the presence of discrete concentrations of normal VWF inside the platelets and within endothelial matrices. The low subject number (n=4) and the treatment scheme for menorrhagia on Days 1, 2, and 3 of menses which might represent rather on-demand than prophylactic treatment may also account for the outcome in this study.

Results from the prospective study component were reported recently.[11] Eleven subjects completed the study. Six subjects had type 2A, and 5 subjects had type 3 VWD. Six subjects presented with epistaxis, 3 with GI bleeding, and 2 with joint bleeding. Seven subjects had dose escalation above the first level. Among the 10 subjects with evaluable bleeding log data, the use of prophylaxis decreased the median ABR from 25 to 6.1 (95% confidence interval [CI] of the rate difference: -51.6 to -1.7), and the median ABR was even lower (4.0; 95% CI: -57.5 to -5.3) when the subjects reached their final dosing level. The authors concluded that this was the first prospective study to demonstrate that prophylaxis with VWF concentrates is highly effective in reducing mucosal and joint bleeding rates in clinically severe VWD.

The results of the VIP study and previous investigations suggest that VWD patients with recurrent bleeding episodes and severe menorrhagia will benefit from a prophylactic VWF replacement therapy. There is evidence that up to 40% of patients with type 3 VWD experience joint bleeding which can lead to hemophilic arthropathy. Other potential indications for prophylaxis include patients with type 2A or 2B VWD with recurrent gastrointestinal bleeding, menorrhagia or frequent epistaxis.[4] Long-term prophylaxis for most patients with type 3 VWD and in some patients with type 1 or 2 VWD, depending on the pattern of bleeding, may be the treatment option of choice. Although the main experience with long-term prophylaxis is with secondary prophylaxis, primary prophylaxis starting at young age is recommended to prevent arthropathy in patients with severe VWD.[12]

However, further studies are needed to develop evidence-based guidelines for prophylactic treatment in VWD.

6.4 Populations to be Studied

A total of approximately 22 eligible, adult subjects with severe VWD (baseline VWF:RCo <20 IU/dL) are planned to be enrolled. Two cohorts of patients will be included: patients currently receiving on-demand VWF treatment (OD subjects) and patients currently on prophylactic treatment with pdVWF (pdVWF switch subjects), and the aim is to have ≥8 subjects in each of the 2 cohorts, with a total of at least 5 type 3 VWD subjects followed for 12 months. Enrolled subjects (i.e., subjects who have signed the informed consent form) will be eligible to participate in the study if they meet all of the inclusion criteria (see Section 9.1) and none of the exclusion criteria (see Section 9.2).

6.5 Findings from Nonclinical and Clinical Studies

The following summarizes the key findings from relevant nonclinical studies as well as from the completed clinical studies **070701** (Phase 1 pharmacokinetics [PK] and safety in VWD), **071001** (Phase 3 safety and efficacy in the treatment of bleeding episodes in VWD), **071101** (Phase 3 efficacy and safety in VWD subjects undergo elective surgical procedures), **071104** (Phase 1 safety and PK in hemophilia A), and **071401** (Phase 3, expanded access in a single subject with VWD). Potential risks and efficacy of rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) are summarized in the following sections. For additional information on nonclinical and clinical Phase 1 results refer to the rVWF (vonicog alfa) IB.

6.5.1 Findings from Nonclinical Studies

6.5.1.1 Primary Pharmacodynamics

Efficacy of rVWF (vonicog alfa) combined with ADVATE (rFVIII, octocog alfa) was shown in VWD animal models, which have also low endogenous FVIII levels. Time to occlusion and stable thrombus formation was assessed in the carotid occlusion model in VWD mice. The results demonstrated that rVWF (vonicog alfa) in combination with ADVATE (rFVIII, octocog alfa) acted efficiently in a dose-dependent manner and had higher efficacy than rVWF (vonicog alfa) alone or plasma derived (pd)VWF. These results were confirmed in an additional study assessing blood loss and survival in a tail tip bleeding model in VWD mice. In a VWD dog, rVWF (vonicog alfa) stabilized canine FVIII in the circulation and significantly reduced the bleeding time.

6.5.1.2 Safety Pharmacology

The anaphylactoid and thrombogenic potential of the co-infusion of ADVATE (rFVIII, octocog alfa) and rVWF (vonicog alfa) and the co-infused product's effects on blood pressure, cardiac and respiratory function and parameters of coagulation activation were investigated in 4 in vivo studies in different animal models. Safety pharmacology studies in rats, guinea pigs, rabbits, and dogs revealed no risks for anaphylactoid and thrombogenic potential of ADVATE (rFVIII, octocog alfa) in combination with rVWF (vonicog alfa). All observations in safety pharmacology studies are considered to lie within the biological variability of animal models or occurred due to known species-specific anaphylactoid effects of excipients.

6.5.1.3 Pharmacokinetics

Pharmacokinetic studies of both rVWF (vonicog alfa) alone and combined with human rFVIII (rVWF+ADVATE) were conducted in VWD mice, VWD dogs, VWD pigs, rats, and cynomolgus monkeys. Human rVWF (vonicog alfa) stabilized the endogenous FVIII in VWD mice, VWD pigs, and VWD dogs. Furthermore, the hypotheses that the area under the curve (AUC) with rVWF alone and rVWF+ADVATE is not inferior to the AUC with pdVWF (Haemate P) was tested and confirmed statistically in normal rats. The PK characteristics of ADVATE (rFVIII, octocog alfa) were not affected by co-administration of rVWF (vonicog alfa) in cynomolgus monkeys. The PK data in the FVIII knock out (k.o.) mice model are inconclusive and might not be relevant for the clinical situation. However, a stabilizing effect of VWF on FVIII could be shown in a double k.o. model in a dose dependent manner.

6.5.1.4 Toxicology

Single dose toxicity studies were conducted in C57BL/6J-mice, VWD mice, rats, rabbits, and cynomolgus monkeys. Rats, rabbits, and cynomolgus monkeys showed no signs of toxicity. Signs of microthrombosis, an exaggerated pharmacological effect, were observed in mice. Mice are not capable of sufficiently cleaving the rVWF (vonicog alfa) subunit as murine disintegrin and metalloproteinase with a thrombospondin type 1 motif, number 13 (ADAMTS13) does not decrease the ultra-large molecular weight multimers of rVWF (vonicog alfa).[13] The observed symptoms of microthrombosis are interpreted as a species-specific exaggerated pharmacological effect. Studies evaluating the safety of repeated administration of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) (daily over 14 days) were performed in a rodent (rat) and non-rodent (cynomolgus monkey) species. Reversible signs of exaggerated pharmacological effects (regenerative anemia, thrombocytopenia, and treatment-related histopathologic changes in the heart, liver, and spleen) were observed in rats that were administered 1400 U VWF:RCo/kg /day + 1080 IU ADVATE/kg/day intravenously once daily for 14 days. Also, these findings are interpreted as a species-specific exaggerated pharmacological effect due to the low susceptibility of human rVWF (vonicog alfa) to cleavage by rodent ADAMTS13.[13] No toxicologically relevant changes were evident for clinical observations, body weight, feed consumption, ophthalmology, urinalysis, coagulation, and serum chemistry parameters, platelet aggregation, and gross pathology. rVWF (vonicog alfa) combined with ADVATE (rFVIII, octocog alfa) was well tolerated in cynomolgus monkeys after daily intravenous (i.v.) (bolus) administration of 100 U VWF:RCo/kg rVWF (vonicog alfa) combined with 77 IU/kg ADVATE (rFVIII, octocog alfa) over a period of 14 days. No adverse effects could be detected in this species.

There were no signs of hemolysis, thrombosis, or thrombocytopenia after repeated intravenous application of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa). Therefore, 100 U VWF:RCo/kg/day rVWF (vonicog alfa) with or without 77 IU/kg ADVATE (rFVIII, octocog alfa) was considered the no observed adverse effect level (NOAEL) in this study, which was the highest dose tested. Anti-drug antibodies, however, were formed in both species and resulted in a significant reduction in drug exposure after 14 applications as compared to a single application. These antibodies substantially reduced the systemic exposure to the test substance as compared to a single dose administration. No adverse effects due to antibody formation were observed in both species.

rVWF (vonicog alfa) combined with ADVATE (rFVIII, octocog alfa) was well tolerated locally and no genotoxic potential was evident after 2 in vitro and 1 in vivo genotoxicity study. A study on the influence of co-administration of VWF and ADVATE (rFVIII, octocog alfa) on the immunogenicity of ADVATE (rFVIII, octocog alfa) in 3 different hemophilic mouse models (E17 hemophilic Balb/c mice, E17 hemophilic C57BL/6J mice, and E17 hemophilic human F8 transgenic mice) showed that rVWF (vonicog alfa) does not negatively impact the immunogenicity of ADVATE (rFVIII, octocog alfa) in any of the three different hemophilic mouse models.

6.5.2 Findings from Clinical Studies

Details on study design, populations enrolled, and safety and efficacy outcomes of the phase 1 studies are presented in Section 6.5.2.1 and Section 6.5.2.2, the phase 3 study in Section 6.5.2.3, and the phase 3 surgery study in Section 6.5.2.4. Information on a single subject with VWD in Study **071401** is presented in Section 6.5.2.5.

6.5.2.1 Study 070701

Phase 1 clinical study **070701** was a multicenter, controlled, randomized, single-blind, prospective 3-step, dose escalation study to investigate safety, tolerability, and PK of rVWF (vonicog alfa) combined at a fixed ratio with ADVATE (VWF:RCo/FVIII:C of 1.3 ± 0.2:1) in adults with severe VWD.[14] Subjects were enrolled in sequential cohorts in a dose escalating manner: Cohort 1, 2, and 3 received a single intravenous infusion of rVWF:ADVATE at the following doses: 2 IU/kg VWF:RCo (Cohort 1), 7.5 IU/kg VWF:RCo (Cohort 2), and 20 IU/kg VWF:RCo (Cohort 3). Subjects in Cohort 4 received a single intravenous infusion of rVWF:ADVATE and pdVWF/ADVATE at 50 IU/kg VWF:RCo in random order.

The primary endpoint was the tolerability and safety after single dose injections of rVWF:ADVATE at 2, 7.5, 20, and 50 IU/kg VWF:RCo for up to 30 days after the last IP infusion. The data generated in this phase 1 study suggest that rVWF:ADVATE up to the highest investigated dose of 50 IU/kg VWF:RCo is well tolerated and safe in adults with severe VWD. No thrombogenic risk or thrombotic thrombocytopenic purpura (TTP)-like syndrome was observed, and no neutralizing antibodies to VWF or FVIII were identified. There were no deaths or other serious adverse reactions, and no infusions were interrupted or stopped due to an AE. Overall, the reported AE profile was similar between the recombinant and plasma-derived concentrates.

Secondary endpoints were the PK assessment of VWF:RCo, von Willebrand factor antigen (VWF:Ag) and multimeric composition of rVWF (vonicog alfa) as well as FVIII:C at standardized time points after single injections of rVWF:ADVATE and pdVWF:FVIII.

The median VWF:RCo terminal half-life ($T_{1/2}$) of rVWF (vonicog alfa) at the 50 IU/kg dose was 16 hours. $T_{1/2}$ with pdVWF:FVIII at the same dose level appeared shorter at 12.58 hours, however, the limits of the 90% CI were similar (11.73 to 17.7 hours vs. 11.87 to 18.03 hours). The median $T_{1/2}$ of VWF:RCo were shorter with the lower investigated doses: 7.13 hours and 13.23 hours with the 7.5 IU/kg and 20 IU/kg doses, although these data were derived from a much smaller number of subjects.

In consequence of the missing ADAMTS13 cleavage, ultra-large molecular weight (ULMW) multimers are contained in the rVWF (vonicog alfa) final product. The immediate cleavage of these ultra-large multimers by ADAMTS13 upon release into the circulation could be demonstrated applying sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE)/Immunoblot with polyclonal anti-VWF antibodies to detect the resulting rVWF (vonicog alfa) subunit cleavage fragments.

Overall the data generated in this phase 1 study suggest that rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) is well tolerated and safe in adults with severe VWD.

6.5.2.2 Study 071104

This study was a prospective, uncontrolled, non-randomized, multicenter proof of concept study to assess safety and PK of the addition of rVWF (vonicog alfa) to ADVATE (rFVIII, octocog alfa) treatment in 12 evaluable subjects with severe hemophilia A. All subjects underwent 3 PK analyses: the first after infusion with ADVATE (rFVIII, octocog alfa) alone, the second after infusion with ADVATE (rFVIII, octocog alfa) plus 10 IU/kg rVWF (vonicog alfa) and the third after infusion with ADVATE (rFVIII, octocog alfa) plus 50 IU/kg rVWF (vonicog alfa).

The PK analysis was performed at intervals of approximately 8 to 14 days. Before each infusion for PK assessment, there was a wash-out period of at least 5 days and the subjects were not actively bleeding.

Primary outcome measures indicate that co-administration of rVWF (vonicog alfa) slightly sustain ADVATE activity with the highest observed ADVATE (rFVIII, octocog alfa) half-life of 13.74 h (CI 11.44 to 16.52) after co-infusion of 50 IU/kg ADVATE plus 50 IU/kg rVWF:RCo.

The highest improvement in ADVATE (rFVIII, octocog alfa) circulating half-life was observed in subjects with VWF:Ag levels below 100% which indicates an association between baseline VWF:Ag levels and ADVATE (rFVIII, octocog alfa) half-life increase.

No treatment related AEs or SAEs were reported. No subject withdrew due to an AE and there were no deaths. No binding antibodies to VWF, CHO, and rFurin were detectable in the confirmatory assay and no signs of a hypersensitivity to rVWF (vonicog alfa) or ADVATE (rFVIII, octocog alfa) antigen were observed. Laboratory values over time did not indicate any potential safety risk for hemophilia A patients treated with rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) in combination.

In summary, the data indicate that rVWF (vonicog alfa) co-administered with ADVATE (rFVIII, octocog alfa) up to the highest dose of 50 IU/kg VWF:RCo is well tolerated and safe in hemophilia A patients.

6.5.2.3 Study 071001

This was a phase 3, multicenter, open-label, part-randomized clinical study to assess the PK, safety, and efficacy of rVWF:rFVIII and rVWF in the treatment of bleeding episodes in adult subjects with severe type 3 and severe non-type 3 VWD.[15] A total of 49 subjects were enrolled (signed informed consent) and screened, 18 subjects were randomized (randomization only applies to Arm 1[PK50 with treatment of BE] and Arm 2 [PK50 only] see below), 37 subjects were treated with IP (all study arms), and 30 subjects completed the study.

The study consisted of 2 parts (Part A and Part B). Part A consisted of PK assessments alone (Arm 2: PK50 only [without treatment of bleeding episodes]), or PK assessments (Arm 1: PK50 and Arm 3: PK80) plus on-demand treatment period(s) of 6 months for bleeding episodes, or on-demand treatment for bleeding episodes only (Arm 4). Except for subjects in arm 2 who completed study after second PK assessment, subjects receiving treatment for PK assessments and/or bleeding episodes in Part A were to be entered into Part B to continue on-demand treatment for bleeding episodes for 6 additional months for a total of 12 months in the study.

The primary outcome measure was the number of subjects with "treatment success" (extent of control of bleeding episodes), which was defined as a mean efficacy rating score of <2.5 for a subject's IP-treated bleeding episodes during the study. The rate of subjects with treatment success was 100% (Clopper-Pearson exact 90% CI: 84.7 to 100.0) for bleeds where the assessments were made prospectively and excluding GI bleeds. Sensitivity analyses confirmed the results of the primary analysis.

Crossover results at 50 IU/kg VWF:RCo showed that the PK profile for rVWF (vonicog alfa) VWF:RCo was independent of administration alone or with rFVIII (ADVATE, octocog alpha) ($T_{1/2}$: 19.4 hours for rVWF and 16.6 hours for rVWF:rFVIII; IR: 1.8 U/dL per IU/kg infused for both rVWF and rVWF:rFVIII; mean residence time (MRT): 26.7 hours for rVWF and 25.2 hours for rVWF:rFVIII). FVIII levels increased substantially with a median peak at 24 hours of 111.0 U/dL for rVWF:rFVIII and 86.0 U/dL after rVWF alone, indicating that rVWF (vonicog alfa) induces a sustained increase in endogenous FVIII activity. The rVWF (vonicog alfa) PK profile was comparable at 50 IU/kg and 80 IU/kg VWF:RCo, and repeated PK at 80 IU/kg VWF:RCo showed close agreement between pretreatment and end-of-study results.

Further analysis of the PK data from the **071001** study supports the initial use of 50 IU/kg twice weekly for prophylaxis dosing in the present study for those subjects who are moving from on-demand to prophylaxis. Using 50 IU/kg for PK measurements, subjects in the **071001** study exhibiting a $T_{1/2}$ for rVWF of 14, 16, or 19 hours had rVWF plasma concentrations at 72 hours after administration of 2.55, 4.01, and 6.49% above baseline, respectively, and plasma concentrations at 96 hours after administration of 0.78, 1.40, and 2.71% above baseline, respectively. In this context it should be noted that subjects in the present study who have significant spontaneous bleeding while on twice weekly prophylaxis will have their regimen increased to 3 times per week based on clear criteria for different bleeding locations (for details see Section 8.6.4.3.1). Subjects in the present study who are switching from prophylaxis with a pdVWF product will begin on rVWF (vonicog alfa) using their same weekly total dose in IU/kg VWF:RCo used during their pdVWF prophylaxis divided into twice weekly infusions (for details see Section 8.6.4.3).

A total of 125 AEs occurred in 25/37 (67.7%) subjects (62/318 infusions [19.5%]) during or after infusion with IP. Of these, 116/125 were non-serious (all mild or moderate; none were severe), and 9 SAEs were reported in 7 subjects. Of 125 total AEs, 38 were temporally associated with IP; 8 AEs were considered causally related to IP: 6 non-serious related AEs (tachycardia, infusion site paraesthesia, electrocardiogram [ECG] t-wave inversion, dysgeusia, generalized pruritis, and hot flush) occurred in 4 subjects, and 2 related SAEs (chest discomfort and increased heart rate) occurred in 1 subject. No deaths occurred during this study.

None of the subjects developed anti-VWF or anti-FVIII neutralizing antibodies and no binding antibodies to VWF or rFurin, or antibodies against CHO protein or anti-Murine IgG were observed. No clinical or subclinical signs or symptoms of a thrombogenic event were observed in this study. Following an initial increase in ultralarge VWF multimers after administration of rVWF (vonicog alfa), a notable decrease in the proportion of large VWF multimers occurred between 12 and 24 hours post infusion, due to degradation by the endogenous ADAMTS13 followed by a continued decline until the end of the 96-hour follow-up period.

Overall, the data support the safe and effective use of rVWF (vonicog alfa) with or without rFVIII (ADVATE, octocog alpha) in the treatment of bleeds in patients with VWD.

6.5.2.4 Study 071101

This was a phase 3, prospective, open-label, multicenter clinical study to evaluate efficacy and safety of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) in elective surgical procedures in adult subjects with severe VWD. A total of 24 subjects were enrolled (signed informed consent) and screened, 15 subjects were treated with rVWF (vonicog alfa), and 15 subjects completed the study.

Eleven subjects underwent a PK assessment by infusion of 50 ± 5 IU/kg rVWF:RCo at an infusion rate of up to 4 mL/min. 12 to 24 hours before surgery, subjects received a dose of 40 to 60 IU/kg rVWF:RCo. Within 3 hours prior to surgery, the subject's FVIII:C levels were assessed with a target of 30 IU/dL for minor and oral surgeries and 60 IU/dL for major surgeries. Within 1 hour prior to surgery, subjects received a dose of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) (depending on the target FVIII:C levels at the 3 hour assessment). VWF and FVIII IR and $T_{1/2}$ for each subject, when known, were used to guide the initial dose and subsequent doses.

The primary outcome measure was the overall assessment of hemostatic efficacy assessed by the investigator (hemophilia physician) 24 hours after last perioperative IP infusion or at completion of day 14 visit, whichever occurred earlier, and was summarized by the percentage of subjects in each efficacy category ("excellent", "good", "moderate" and "none"). Point estimate and corresponding 90% two-sided exact CI was calculated for the rate of subjects with an overall assessment of hemostatic efficacy. All 15 subjects treated with rVWF (vonicog alfa) (with or without ADVATE) for major (10), minor (4), and oral (1) elective surgical procedures had overall hemostatic efficacy ratings of "excellent" or "good". Most (73.3%) subjects had "excellent" overall hemostatic efficacy ratings; of these, 7 underwent major surgery and 4 underwent minor surgery. The remaining 26.7% subjects had "good" overall hemostatic efficacy ratings: 3 underwent major surgery and 1 underwent oral surgery. All 8 subjects with VWD Type 3, the subtype classified as absolute VWF deficiency, had overall hemostatic efficacy ratings of "excellent" (87.5%) or "good" (12.5%).

Intraoperative hemostatic efficacy ratings were also rated as "excellent" or "good" for all 15 treated subjects. Most (86.7%) subjects had "excellent" intraoperative hemostatic efficacy ratings; of these, 8 underwent major surgery, 4 underwent minor surgery, and 1 underwent oral surgery. Two (13.3%) subjects who underwent major surgery had "good" intraoperative hemostatic efficacy ratings. Intraoperative hemostatic efficacy was rated as "excellent" or "good" for all subjects with VWD Type 3: "excellent" for 7 (87.5%) subjects and "good" for 1 (12.5%) subject.

Only 1 subject received an intraoperative dose of rVWF (18.1 IU/kg) and ADVATE (8.1 IU/kg). The median daily postoperative weight-adjusted dose of rVWF (vonicog alfa) (with or without ADVATE) was 23.5 IU/kg on postoperative Day 1 (n=3) and 25.5 IU/kg on postoperative Day 14 (n=2). In subjects treated with rVWF:ADVATE, the daily postoperative weight-adjusted dose was 16.9 IU/kg rVWF and 7.6 IU/kg ADVATE on postoperative Day 1 (n=1) and decreased to 50.8 IU/kg rVWF and 7.6 IU/kg ADVATE on postoperative Day 7 (n=1). For subjects treated with rVWF alone, the median weight-adjusted dose (Q1, Q3) of rVWF was 35.4 IU/kg on postoperative Day 1 (n=2) and decreased to 23.7 IU/kg on postoperative Day 7 (n=4) and 25.5 IU/kg on postoperative Day 14 (n=2).

A total of 11 subjects were evaluated for PK in the study. As expected, postinfusion increases in concentrations of VWF:RCo, VWF:Ac, VWF:Ag, and VWF collagen binding (VWF:CB) were observed. Mean values for VWF:RCo were as follows: AUC0-∞/dose was 37.50 hours*IU/dL per IU/kg infused; AUC0-72h/dose was 34.08 hours*IU/dL per IU/kg infused; T1/2 was 17.83 hours; MRT was 24.32 hours; CL was 0.03117 dL/hour/kg; and volume of distribution at steady state (Vss) was 0.6837 dL/kg. Median values for VWF:RCo were as follows: AUC0-∞/dose was 32.94 hours*IU/dL per IU/kg infused; AUC0-72h/dose was 31.70 hours*IU/dL per IU/kg infused; T1/2 was 14.62 hours; MRT was 21.80 hours; CL was 0.03036 dL/hour/kg; and Vss was 0.7078 dL/kg. The VWF:RCo activity was consistent with that previously observed in clinical studies 071001 and 070701.

rVWF (vonicog alfa) was safe and well tolerated in adults with severe VWD undergoing major, minor, and oral elective surgical procedures. Of the 12 total treatment-emergent AEs (TEAEs) that occurred during the study, 2 deep vein thrombosis events (1 non-serious and 1 serious, as a part of one case) reported in one subject, who underwent total hip replacement surgery and who had concurrent condition of obesity, was assessed by the sponsor as possibly causally-related to study treatment. None of the TEAEs were either a severe allergic or hypersensitivity reaction or developed due to a severe allergic reaction.

One subject with VWD Type 3 who had an intraoperative transfusion of packed red blood cells during total knee replacement surgery tested positive for binding antibodies to VWF on postoperative Day 7 through study completion. No subjects developed neutralizing antibodies to rFVIII or binding antibodies to CHO, rFurin, or murine IgG.

In summary, the data support the safe and effective use of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) in achieving intra- and post-operative hemostasis in adult subjects with severe VWD undergoing major, minor, and oral elective surgical procedures.

6.5.2.5 Study 071401: Single Subject with von Willebrand Disease

One subject who exhibited allergic reactions to currently marketed pdVWF products was treated in the single-subject study **071401** with rVWF (vonicog alfa) only for the bleed treatment of continued hematuria, and for biopsy and surgical resection of a left-kidney mass.

For the initial rVWF (vonicog alfa) infusion, the subject received a test dose of 5% of the total dose of 60 IU/kg rVWF:RCo at an infusion rate of 1 mL/min. After a 10 to 15-minute observation period, no adverse symptoms or signs were noted and the subject received the remaining 95% of the total dose. The subject was monitored for any signs of an allergic reaction, and none were noted. Treatment with rVWF (vonicog alfa) every 12 to 24 hours was to continue at the discretion of the investigator based on VWF levels and clinical symptomatology. The subject had an excellent response and recovery, which allowed for daily dosing of rVWF (vonicog alfa) and, within 24 hours, the subject's bleeding had stopped. Daily dosing of rVWF (vonicog alfa) was maintained and the subject received his last dose on [redacted].

The subject also received rVWF (vonicog alfa) for 7 days for prophylaxis for surgery (surgical resection of a left-kidney mass). The subject experienced no hemorrhagic complications and no AEs that were considered related to the use of rVWF (vonicog alfa).

6.6 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

Current treatment of VWD patients relies on desmopressin and VWF products manufactured from pooled human plasma. Human VWF produced by recombinant technology could offer a new perspective in treatment of VWD. The benefit for the individual subject is anticipated to be significant during this clinical study. He/she may benefit from a product that minimizes excessive FVIII administration and thus allowing individualized dosing of VWF at optimal levels. Variations in VWF multimeric composition may lead to variability with respect to treating or preventing bleeds in VWD subjects, especially mucosal bleeds which are especially problematic. rVWF (vonicog alfa) product manufactured by Baxalta consistently contains ULMW VWF multimers due to the fact that the product has not been exposed to ADAMTS13.

The initial presence of these ULMW VWF multimers, which are subsequently cleaved by the subject's endogenous ADAMTS13, may result in improved platelet and collagen binding and therefore provide more predictable treatment outcomes.

By using a recombinant product, the risk of transmission of adventitious agents and other blood-borne pathogens associated with the use of products of human or animal origin has been eliminated. At this stage of product development, the key societal benefit is a better understanding of advanced treatment options for VWD and enhanced product availability.

These benefits outweigh the following identified or potential risks of rVWF (vonicog alfa):

- allergic-type hypersensitivity reactions as with any intravenous protein product
- the occurrence of thromboembolic events
- the development of neutralizing antibodies to VWF

Refer to the IB for further details on benefits and risks of the IP.

6.7 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996, with Addendum E6(R2) dated Nov 2016 EMA/CHMP/ICH/135/1995), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives 2001/20/EC and 2005/28/EC, the Declaration of Helsinki and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

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

7.2 Primary Objective

The primary objective of this study is to prospectively evaluate the 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.

7.3 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 FVIII activity

7.4 Exploratory Objectives

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

8. STUDY DESIGN

8.1 Overall Study Design

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

Subjects transitioning from on-demand treatment (OD subjects) or subjects switching from prophylactic treatment with pdVWF (pdVWF switch subjects) will receive prophylactic treatment with rVWF (vonicog alfa) for a 12-month period. The dose will be 50 ± 10 IU/kg rVWF twice weekly for OD subjects or will be based on their prior pdVWF dose for pdVWF switch subjects, and 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 Section 8.6.4.3).

The overall duration of prophylactic treatment with rVWF per subject will be 12 months.

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 Section 8.6.4.4.2).

The overall study design is illustrated in Figure 1.

8.2 Duration of Study Period(s) and Subject Participation

The overall duration of the study is approximately 27 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The subject participation period is approximately 15 months from enrollment to completion (i.e, last study visit), unless the subject is prematurely discontinued.

8.3 Outcome Measures

8.3.1 Primary Outcome Measure

8.3.1.1 Efficacy

- Annualized bleeding rate (ABR) for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa)

8.3.2 Secondary Outcome Measures

8.3.2.1 Additional efficacy of Prophylactic Treatment with rVWF (vonicog alfa)

- ABR percent reduction success for OD subjects defined as at least 25% reduction of ABR for spontaneous (not related to trauma) bleeding episodes during rVWF (vonicog alfa) prophylaxis relative to the subject's own historical ABR during on-demand treatment
- ABR preservation success for pdVWF switch subjects 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 during prophylactic treatment with pdVWF
- Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 bleeding episodes during the 12-month 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
- Spontaneous ABR 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)

8.3.2.2 Safety

- AEs: incidence, severity, causality
- Thromboembolic events
- Hypersensitivity reactions
- Development of neutralizing antibodies to VWF and FVIII
- Development of total binding antibodies to VWF and FVIII
- Development of binding antibodies to CHO proteins, mouse immunoglobulin G (IgG) and rFurin
- Clinically significant changes in vital signs and clinical laboratory parameters relative to baseline

8.3.2.3 Pharmacokinetics (PK) and Pharmacodynamics (PD)

- PK parameters after a washout for on-demand subjects: incremental recovery (IR), $T_{1/2}$, 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 VWF:Rco activity, VWF:Ag, VWF:CB activity.
- PD parameters after a washout for on-demand subjects: C_{max}, T_{max}, and $AUC_{0-tlast}$ as measured in FVIII activity by the 1-stage clotting assay (FVIII:C).
- PK parameters at steady state for on-demand and switch subjects: area under the concentration versus time curve from 0 to end of the partial dosing interval ($AUC_{0-tau;ss}$), 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. PK parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.
- PD parameters at steady state for on-demand and switch subjects: $AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$ as measured in FVIII activity by the 1-stage clotting assay. PD parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.
- Time course of FVIII clotting activity (FVIII:C) levels.

8.3.3 Exploratory Outcomes Measures

8.3.3.1 [redacted]

- [redacted]
- [redacted]

[redacted]

8.3.3.2 [redacted]

[redacted]

8.3.3.3 [redacted]

[redacted]

8.3.3.4 [redacted]

[redacted]

8.4 Randomization and Blinding

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

8.5 Study Stopping Criteria

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 (eg, 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.

The sponsor ultimately 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.

8.6 Investigational Product(s)

8.6.1 Packaging, Labeling, and Storage

8.6.1.1 rVWF (Recombinant von Willebrand Factor, vonicog alfa)

rVWF (vonicog alfa) will be packaged in boxes with 2 glass vials, one containing the rVWF powder, and the second vial containing the diluent (water for injection). Further details are provided in the IB and Pharmacy Manual. The rVWF label will include, at a minimum, the actual VWF:RCo potency and the date of expiration.

rVWF (vonicog alfa) is a powder that should be stored refrigerated (2-8°C [36-46°F]) . Deviations from the storage condition have to be communicated and followed up with the sponsor. Inadequately stored product will have to be placed in quarantine and may only be used after written IP administration authorization by the sponsor. After removal of the product from the refrigerator the product must not be returned to the refrigerator. The reconstituted product has to be used immediately (at least within 3 hours). rVWF (vonicog alfa) must not be used beyond the expiration date printed on the vial label. Avoid freezing at all times.

8.6.1.2 rFVIII (Recombinant Factor VIII, octocog alfa /ADVATE)

ADVATE (rFVIII, octocog alfa) will be packaged in boxes with 2 glass vials, one containing the lyophilized rFVIII, and the second vial containing the diluent. Further details are provided in the IB and Pharmacy Manual. The ADVATE label will include, at a minimum, the actual FVIII:C potency and the date of expiration.

ADVATE (rFVIII, octocog alfa) should be refrigerated (2-8°C [36-46°F]) in powder form and should not be used beyond the expiration date printed on the vial.
Deviations from the storage condition have to be communicated and followed up with the sponsor. Inadequately stored product will have to be placed in quarantine and may only be used after written IP administration authorization by the sponsor. After removal of the product from the refrigerator the product must not be returned to the refrigerator and has to be used immediately. Avoid freezing at all times.

8.6.2 Reconstitution

The reconstitution procedures for both rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) products are detailed in the Pharmacy Manual.

8.6.3 Administration

Following reconstitution, rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) (in case of bleeding episode treatment) should be administered to study subjects at room temperature and within 3 hours of reconstitution. The reconstituted rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa), should be inspected for particulate matter and discoloration prior to administration, whenever the solution and container permit. The solution should be clear and colorless in appearance. If not, do not administer the product. Plastic syringes provided by the sponsor must be used since coagulation factors tend to stick to the surface of glass syringes.

Investigational product infusions should be given at a slow enough rate to ensure the subject's comfort. The rate should not exceed 4 mL/minute The investigator/ subject shall ensure that no visible residual volume remains in the syringe(s) and that the complete content is administered. Upon completion of the infusion, the butterfly catheter should be flushed with at least 2 mL of saline solution. In case of a (central) venous access device, the flush should be with at least 10 mL of saline solution. The IP infusions should be administered over a duration of 2 to 20 minutes, depending on the volume.

Only the actual potencies of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) as stated on the vial labels and described in the Pharmacy Manual should be used.

A variation of up to 10% of the intended dose for prophylactic infusions and of the intended dose for treatment of bleeding episodes is permissible and the exact dose should be recorded on the Case Report Form (CRF). Using of partial vials is not allowed.

At study visits where recovery analysis is being done, vials with the same lot numbers should be used throughout the PK IP infusion per subject.

For treatment of bleeding episodes, sequential administration will be done: separate syringes of the appropriate dose of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) will be prepared for sequential infusion. rVWF (vonicog alfa) should be infused first sequentially followed preferably within 10 minutes by infusion of ADVATE (rFVIII, octocog alfa). Only the actual potencies of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) as stated on the vial labels and described in the Pharmacy Manual should be used.

The final dose of rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) should be at a ratio of 1.3:1 ± 0.2.

8.6.4 Description of Treatment

8.6.4.1 PK-Assessment Treatment

For on-demand subjects, two PK assessments will be performed: an initial PK assessment after a wash-out period and a steady state PK assessments at the end of the study. The IP infusion for the initial PK assessment is scheduled on the baseline visit, which should be within 42 days after the completion of screening procedures and confirmation of eligibility. At the baseline visit the subjects will receive a dose of 50 ± 5 IU/kg rVWF:RCo for PK assessment. 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). A washout period of at least 5 days is required prior to infusion of rVWF (vonicog alpha) for PK assessment. The 2nd PK assessment for on-demand subjects will be performed at steady state at the end of the study (see Section 11.6). Subjects previously enrolled in rVWF studies **070701**, **071001** or **071101** and having previously undergone PK assessments in these studies are required to repeat the PK assessment due to different dose and time points used in these former studies.

For pdVWF switch subjects, two steady state PK assessments will be performed. The 1st PK will be assessed shortly after reaching steady state, which is expected to be 11 days after the 1st prophylactic dose for majority of the subjects, around the prophylactic dose #5-6. The 2nd PK will be at the end of the study.

For steady state PK, 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) as long as it won't interfere with subject's the normal dosing schedule, otherwise the 96 hr sampling can be omitted (see Section 11.6). Final sample for PK analysis should be taken before next dose is administered.

8.6.4.2 Prophylaxis Initiation Treatment

The rVWF (vonicog alfa) prophylaxis initiation treatment visit will coincide with the 96 ± 2 h initial PK assessment for on-demand subjects. For pdVWF switch subjects, the rVWF (vonicog alfa) prophylaxis initiation treatment visit should occur within 42 days after the completion of screening procedures and confirmation of eligibility. At this visit subjects will receive their prophylaxis initiation dose. The prophylaxis doses are described in Section 8.6.4.3.

The subject will be trained on IP reconstitution and administration and may then qualify for home treatment (see Section 8.6.4.3.2). Refer toTable 6 (a/b) for study procedures and Table 8 (a/b) for clinical laboratory assessments.

8.6.4.3 Prophylaxis Treatment

For on-demand subjects, the standard prophylactic dose is 50 ± 10 IU/kg rVWF:RCo, which may be increased up to 80 IU/kg. All on-demand subjects will initially receive rVWF (vonicog alfa) twice per week (Table 1, Schedule A). Examples of all dosing schedules are provided in Table 1.

For pdVWF switch subjects, the weekly dose (IU/kg) of IP for each patient 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 (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 (Table 1, Schedule B). A once weekly dose regimen will be allowed after switch to rVWF (vonicog alfa) only if the patient has been on a once weekly dose regimen with pdVWF.

Table 1
rVWF (vonicog alfa) Dosing Schedule Examples: Schedules A and B

Example	M	T	W	Th	F	Sat	Sun	M	T	W	Th	F	Sat	Sun
Schedule A	X				X			X				X		
Schedule B	X		X			X		X		X			X	

The prophylaxis dose may be further individualized within the range based on:

- available historical PK data
- type and severity of bleeding episodes the subject has experienced in the past and
- monitoring of appropriate clinical and laboratory measures

The individualized prophylaxic dose assignment will have to be agreed with the sponsor in advance, and the rationale should be well documented.

8.6.4.3.1 Adjustment of Dose or Dose Interval

In general, the dose and/or dose interval for each subject should not be changed unless prompted by clear medical needs. Dose and frequency adjustments should be agreed with the sponsor in advance unless it constitutes an urgent safety measure. The rationale for dosing adjustments needs to be documented in the subject's medical record.

For both OD and switch patients, dose escalations (not exceeding the upper dose limit of 80 IU/kg rVWF:RCo) and increase of dose frequency will only be allowed in case of insufficient therapeutic response with breakthrough bleeding episodes. The criteria for dose and/or frequency escalation are specific to each bleeding indication but, overall, involve 1 significant breakthrough bleeding episode despite the subject being compliant with scheduled prophylaxis treatment. For switch patients who require a dose escalation due to a breakthrough bleed, the frequency should be kept the same but the dose (IU VWF:RCo per infusion) should be increased up to 80 IU VWF:RCo. Following that, increases in frequency may be considered upon consultation with the Sponsor. For on demand subjects who require a dose escalation, at the discretion of the PI upon consultation with the Sponsor, the frequency may be kept the same but the dose (IU VWF:RCo per infusion) should be increased up to 80 IU VWF:RCo. If this proves to be insufficient, then the dosing frequency may be increased in these subjects. Table 2 presents the criteria for dosing escalation per each bleeding indication taken 50 ± 10 IU VWF:RCo/kg twice weekly dose as an example of subject's assigned starting dose. The criteria are applicable for both OD and switch subjects who were initially assigned to twice weekly dosing. Subjects entering the study will begin prophylaxis treatment according to Schedule A (Table 1) and will remain at this dose and frequency until meeting the criteria for escalation to the next higher schedule: for example, from 2 infusions of 50 ± 10 IU VWF:RCo/kg/week to 3 infusions of 50 ± 10 IU VWF:RCo/kg/week (Schedule B) to achieve an adequate therapeutic response. If a subject started with a weekly dose (possible for switch subjects), similar criteria would apply except that the subject will be excalated to twice weekly dosing if frequency change is necessary.

Table 2
Criteria for Escalation Specific to Each Bleeding Indication

	Schedule A	Schedule B
Joint bleeding	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a spontaneous joint bleeding episode occurs while on this regimen, the subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B following its resolution	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
GI bleeding	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a severe GI bleeding episode, i.e., requiring red blood cell transfusion, occurs while on this regimen, the subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B following its resolution	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Menorrhagia	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) on days 1 and 2 of menses for 2 cycles. Menstrual flow will be monitored by the PBAC score. If the average pictorial chart score is > 185, then the subject will escalate to up to 80 IU/kg or, if necessary, to Schedule B	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) on days 1, 2, and 3 of menses. Menstrual flow will be monitored by the PBAC score.
Epistaxis	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. The subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B in the event of 1 occurrence of breakthrough bleeding requiring intervention such as iron replacement therapy, transfusion, packing, hospitalization; or 2 bleeding events that require treatment with factor replacement	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Oral and Other Mucosa	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. The subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B in the event of 1 occurrence of breakthrough bleeding requiring intervention such as iron replacement therapy, transfusion, packing, hospitalization; or 2 bleeding events that require treatment with factor replacement.	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Muscle and Soft Tissue	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a spontaneous bleeding episode occurs while on this schedule, the subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B following its resolution.	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.

Abbreviations: GI: gastrointestinal; PBAC: Pictorial Blood Assessment Chart.

If a subject does not adequately respond to rVWF (vonicog alfa) therapy, he/she will be evaluated for the presence of neutralizing and total binding anti-VWF antibodies (see Section 12.9.3.2).

If a subject experiences a bleed while receiving rVWF (vonicog alfa) three times per week, the investigator should treat the bleed with rVWF (vonicog alfa) at doses up to 80 IU VWF:RCo/kg at a frequency determined by the investigator until the bleed resolves. Upon resolution of the bleeding event, the subject will return to their assigned prophylaxis regimen.

It is essential for the success of this study that the subjects adhere to treatment regimens. Therefore, procedures for monitoring subject's compliance are implemented (see Section 10.7).

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. For example, a subject routinely infuses IP on Monday and Thursday, he/she misses the Monday time point and therefore may infuse the IP on the next day (Tuesday) and thereafter proceed with infusing the IP on Thursday (considering a minimum 12 hours between the infusions) and return to the initial schedule.

If more than 30% of infusions of IP are missed within the visit interval of 3 months the subject will be discontinued from the study (see Section 9.4).

8.6.4.3.2 General Instructions for Home Treatment for Prophylaxis

At the discretion of the investigator, a subject may be considered suitable for home treatment only after the subject has received at least 1 infusion of IP in the clinic, either during planned prophylactic IP exposure or during the treatment of bleeding episodes, and meets the following additional criteria:

1. Fully understands the concept of a clinical study and related documentation (documented training of at least 30 minutes),
2. Has a history of previous experience with home treatment including self-administration and treatment with VWF containing concentrates,
3. Has adequate time for initial training of the study drug preparation (preparation, mixing and infusion of the IP(s) (documented training of at least 30 minutes).

This applies both to subjects who were on prior on-demand treatment and to subjects switching form prophylaxis with pdVWF. In the event a healthcare professional is required to administer IP, he/she must be trained and qualified by the investigator on the above procedures prior to the decision for home treatment. A Subject Guideline detailing all instructions and information listed above will be provided to each subject.

8.6.4.4 Treatment of Bleeding Episodes

8.6.4.4.1 General Instructions for Home Treatment of Bleeding Episodes

If a subject experiences a bleeding episode, he/she should contact the study site immediately and the site investigator should provide instructions on the treatment regimen. If the subject initiates the treatment at home, he/she should at least follow up with the study site if a visit is needed as per the standard of care at the center.

In the event a healthcare professional is required to administer treatment at the subject's home, he/she must be trained and qualified by the site investigator on the above procedures prior to the decision for home treatment. Once a subject has received 1 infusion of rVWF (vonicog alfa) in the clinic (either during planned IP exposure or during the treatment of a bleeding episode) and meets the criteria for home treatment, the treatment of bleeding episodes with IP can be conducted at home (see Section 8.6.4.3.2).

If a subject is not qualified for home treatment, rVWF (vonicog alfa) infusions must be administered at the study site.

If a subject experiences a bleeding episode that requires treatment between the screening and the prophylaxis initiation visit, the subject will be treated with IP (rVWF with or without ADVATE). Treatment with IP must occur at the study site unless the subject has previously qualified for home treatment with rVWF (vonicog alfa). If rVWF (vonicog alfa) treatment is not feasible, the subject may use his/her standard of care, such as commercial pdVWF/FVIII products. In any case a washout period of at least 5 days is required prior to rVWF (vonicog alfa) PK infusion at the initial PK assessment visit for on-demand subjects.

If a subject experiences a bleeding episode requiring treatment during the PK assessment, rVWF (vonicog alfa) should be used to treat the bleed. Blood draws for PK assessment will be stopped and the PK assessments will be repeated once the bleed has resolved and the subject is free of any symptoms related with the bleeding episode. Dose and frequency of rVWF (vonicog alfa) infusions or any other replacement therapy to stop the bleed should be recorded in the electronic Case Report Form (eCRF), and the reason for the use of any non-IP product or therapy should be documented.

8.6.4.4.2 Dosing Recommendations for Treatment of Bleeding Episodes

If an acute bleeding episode occurs, the subject will be treated with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa). It is the sponsor's opinion that, in many cases, treatment with ADVATE (rFVIII, octocog alfa) may not be necessary, since rVWF (vonicog alfa) prophylaxis will serve to increase endogenous FVIII levels. However, if endogenous FVIII is below 30-40 % or is unknown and cannot be estimated from the subject's PK study, an infusion of rVWF: ADVATE at an rVWF: ADVATE ratio of 1.3:1± 0.2 should be administered initially. Subsequent infusions should be with rVWF:RCo 40 to 60 IU/kg with or, in many cases,without 30 to 45 IU/kg ADVATE (only to be administered if plasma FVIII levels fall below 30 IU/L during the treatment period). Dosing may be adjusted downward or upward up to 80 IU/kg rVWF at the treating physician's discretion based upon the subject's prior history, PK and other factors.

If FVIII levels are not available, dosing is at the discretion of the investigator based upon the individual subject's PK data. Using ADVATE (rFVIII, octocog alfa) in addition to rVWF (vonicog alfa) in subsequent doses carries the risk of an excessive rise in FVIII:C. Therefore, reduced doses of ADVATE (rFVIII, octocog alfa) and/or prolongation of the dose interval should be considered.

The following is general guidance and the sponsor's suggestion for treatment of breakthrough bleeds, however each PI will determine the treatment based on the local acceptable practice how to monitor and adjust treatment for a bleeding episode. An effort should be made to discuss with the sponsor (or sponsor's delegate) the treatment strategy.

In general the aim of the initial dose should be full replacement of VWF with VWF:RCo levels of >0.6 IU/ml (60%) and FVIII:C of >0.4 IU/mL (40%). In major bleeding episodes, subsequent doses should keep the trough level of VWF:RCo >50% for 3 days and then as deemed necessary by the investigator for subsequent days. In moderate bleeding episodes, the dose and trough level may be reduced to >30% for as long as deemed necessary by the investigator. Treatment for minor bleeding episodes will generally consist of only 1 or 2 doses of rVWF (vonicog alfa) IP.

If the VWF:RCo level is above 150%, a planned treatment should be delayed by at least 12 hours; if the VWF:RCo level is above 200%, a planned treatment should be delayed by at least 24 hours. In either case, a lower subsequent dose (e.g., 20 IU/kg VWF:RCo) may be appropriate.

Dosing recommendations are listed in Table 3.

Dosage must be individualized based on the subject's weight, VWD type, and the severity of the bleeding episode, as well as on monitoring of appropriate clinical and laboratory measures. In the phase 1 study **070701**, 1.0 IU/kg VWF:RCo raised the circulating level of VWF:RCo by 0.017 IU/mL (1.7 %). In the same study, the observed mean half-life for rVWF (vonicog alfa) was 19.3 hours, with a standard deviation of 10.9 hours.

Table 3
rVWF:RCo Dosing Recommendations for the Treatment of Bleeding Episodes Due to VWD

Classification of VWD	Hemorrhage	Dosage (IU VWF:RCo/kg BW)
Type 1 • Severe (Baseline VWF:RCo activity typically <20%)	Minor (e.g., epistaxis, oral bleeding, menorrhagia[a])	40 to 50 IU/kg (1 or 2 doses)
	Major (e.g., severe or refractory epistaxis, menorrhagia*, GI bleeding, CNS trauma, hemarthrosis, or traumatic hemorrhage)	Initial dose 50 to 75 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment
Type 2 (all variants) and Type 3	Minor (clinical indications above)	40 to 50 IU/kg (1 or 2 doses)
	Major (clinical indications above)	Initial dose of 60 to 80 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment

[a] Menorrhagia is defined as excessive bleeding during menstruation. A diagnosis of menorrhagia will be defined by a prospectively completed Pictorial Blood Assessment Chart (PBAC) score >185 and normal cervical cytology or requiring use of a VWF-containing concentrate for treatment of excessive menstrual bleeding for at least one menstrual cycle during the prior year.

Variances of up to 10% in dosing are permissible during treatment of bleeding episodes, but rounding to the nearest vial size should be avoided.

Subjects with non-neutralizing binding anti-VWF antibodies should initially be treated with a dose known to be efficacious based on the subject's medical treatment history which may differ from the recommendations provided in Table 3. Subjects should be monitored for lack of efficacy as well as for FVIII (mandatory), VWF:RCo (mandatory), and VWF:Ag (optional where testing is not available) levels after 3 to 6 hours. Re-dosing with rVWF (vonicog alfa) in combination with ADVATE (rFVIII, octocog alfa) using the same (initial) dose and adaptation of the dosing frequency should be considered until cessation of the bleed, if the FVIII and/or VWF:RCo levels drop below 30%-50% depending on bleeding severity.

The number of subsequent infusions and the dosage levels prescribed will be determined by the investigator on the basis of the clinical severity, response to current therapy, available laboratory data, and the subject's historical treatment for similar bleeding episodes.

8.6.4.5 Treatment of Surgical Bleeding

Subjects enrolled in this study who require surgery or dental procedures will be treated with IP to manage their surgical bleeding then afterwards will resume their prophylactic rVWF (vonicog alfa) treatment schedule. Subjects who at time of screening have an already scheduled surgical intervention are not eligible for participation in the study.

8.6.4.5.1 Major, Minor and Oral Surgery Definition

The following definitions and criteria are used to serve as a guidance for *major, minor and oral surgery*.

Major surgeries generally refer to major orthopedic surgery (e.g., joint replacement, arthroscopic or open synovectomy, arthrodesis, hardware removals like plates or intramedullary nails, etc.), major abdominal surgery (e.g. open or laparoscopic hernioplasty, cholecystectomy, colon or small bowel resection, etc.), major gynecological surgery (e.g. open or laparoscopic myomectomy, hysterectomy, removal of endometriosis, polyps, cysts, adhesiolysis, etc.), major head and neck surgery (e.g.: tonsillectomy, adenoidectomy, rhinoplasty, lymphadenectomy, thyroidectomy, parotidectomy. etc.), any intracranial , cardiovascular or spinal surgery and any other surgery which has a significant risk of large volume blood loss or blood loss into a confined anatomical space. Extraction of impacted third molars is generally also considered major surgery due to the expected difficulty of surgery and the expected blood loss.

Minor surgeries generally refer to interventions such as placement of intravenous access devices, removal of small skin lesions, arthroscopy, gastroscopy, colonoscopy or conisation.

Oral surgeries comprise extractions of fewer than three teeth, if the teeth are non-molars and have no bony involvement.

A summary schedule of visit assessments and laboratory sampling is included in Supplement tables in Section 20.2.1 and Section 20.3.1.

8.6.4.5.2 Preoperative Priming Dose

12- 24 hours prior to surgery, a priming dose with rVWF (vonicog alfa), using the rVWF IR and $T_{1/2}$ for this subject , will be infused to allow the endogenous FVIII levels to raise to at least 30 IU/dL (minor, oral surgery), or 60 IU/dL (major surgery) at the time of the loading dose of rVWF (vonicog alfa) is infused.

As a general guidance a priming dose of 40-60 IU/kg rVWF:RCo will be administered. If not assessed prior to the preoperative priming dose, a IR recovery may be calculated for subjects undergoing minor and oral surgery.

8.6.4.5.3 Preoperative Loading Dose

An rVWF (vonicog alfa) loading dose should be administed within 3 hours before surgery. VWF and FVIII levels should be assessed within 3 hours prior to surgery initiation and results must be available prior to administering the loading dose. If FVIII levels prior to loading dose administration are not at least 30 IU/dL (minor, oral surgery), or 60 IU/dL (major surgery) ADVATE (rFVIII, octocog alfa) will be administered in addition to rVWF (vonicog alfa) in order to raise FVIII:C levels to recommended levels.

The preoperative loading dose will be calculated as the difference in the target peak and baseline plasma VWF:RCo levels divided by the IR (ΔVWF:RCo x BW (kg) /IR). The PK results will be provided prior to the planned surgery. If the IR is not available, assume an IR of 1.7 IU/dL per IU/kg and calculate the initial dose as follows: (100 − baseline plasma VWF:RCo) x BW (kg) / 1.7. For minor and oral surgery, the IR from the Preoperative Priming Dose visit will be used to guide dosing and the target peak is 50-60 IU/dL VWF:RCo and 40-50 IU/dL FVIII. For major surgery, the target peak is 100IU/dL VWF:RCo and 80-100 IU/dL FVIII.

The surgery may only start after normalization of the activated partial thromboplastin time (aPTT).

8.6.4.5.4 Intra- and Postoperative (maintenance) Dosing

After the preoperative loading dose(s), subjects who have not achieved the desired postinfusion recovery will continue to receive rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) as a bolus infusion, depending on VWF and FVIII levels. The peri- and post-operative substitution regimen will be individualized according to the PK results, intensity and duration of the hemostatic challenge, and the institution's standard of care.

Subjects undergoing minor surgery will be infused with rVWF (vonicog alfa) every 12-24 hours or every other day, targerting ≥30IU/dL (rVWF and FVIII) for at least the first 48 hours.

Subjects undergoing oral surgery will be infused with rVWF (vonicog alfa) at least once within the first 8-12 hours, targeting ≥30 IU/dL (rVWF and FVIII).

Subjects undergoing major surgery will be infused with rVWF (vonicog alfa) every 12-24 hours for at least the first 72 hours post-surgery, targeting a VWF:RCo and FVIII:C trough plasma level >50 IU/dL, followed by further treatment post-72 hours for as long as deemed necessary by the Investigator, targeting a VWF:RCo and FVIII:C trough plasma level of ≥30 IU/dL.

Dose modifications based on pre-infusion VWF/FVIII levels will be performed as needed. For subsequent infusions post surgery, in case pre-infusion levels are not available prior to the consecutive infusion in a timely manner, pre-infusion levels from the previous dose may be used by the investigator for dosing guidance.

Peak plasma level guidance is matching to Section 8.6.4.4.2

A schedule of all perioperative visit assessments and laboratory sampling can be found in Supplement tables in Section 20.2.1 and Section 20.3.1.

8.6.4.6 Thrombosis Prophylaxis

Thromboembolic events have been reported in patients who have VWD, especially in the setting of known risk factors for thrombosis including low ADAMTS13 levels. Therefore, subjects who are at risk for developing thromboembolic events should be monitored for early signs of thrombosis, and prophylaxis measures against thromboembolism should be instituted according to current recommendations and standard of care. For all subjects who are VWD patients and are receiving VWF concentrate, attention should be given to avoid exceeding maximal recommended plasma activity levels of VWF:RCo (250 IU/dL) and FVIII (250 IU/dL).

Anticoagulation measures, such as heparin, are acceptable and should follow study site standards. The investigator will record the use and reasons for such measures/agents on the appropriate CRF.

8.6.5 Investigational Product Accountability

The investigator will ensure that the IP(s) is stored as specified in the Pharmacy Manual and that the storage area is secured, with access limited to authorized study personnel. All temperature excursions at the subject's home need to be monitored by the site (please refer to the pharmacy manual). The investigator will maintain records that the IP(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. The IP(s) must be dispensed only at the study site or other suitable location (e.g., infusion center; home, as applicable per study design), as specified in the protocol (see Section 10). Records will be maintained that includes the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

8.7 Source Data

Per ICH E6(R2) on GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). These may be in paper and/or electronic format. Source documents for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

No data will be entered directly onto the CRF.

For additional information on study documentation and CRFs refer to Section 17.2. The use of subject diaries is described in Section 10.5.

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding
   a. Type 1 (VWF:RCo <20 IU/dL) or,
   b. Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2M or,
   c. Type 3 (VWF:Ag ≤3 IU/dL).
2. Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.
3. For on-demand patient group, subject currently receiving on-demand treatment for whom prophylactic treatment is recommended by the investigator.
4. For pdVWF switch patient group, subject has been receiving prophylactic treatment of pdVWF products for no less than 12 months prior to screening.
5. For on-demand patient group, subject has ≥3 documented spontaneous bleeds (not including menorrhagia) requiring VWF treatment during the past 12 months.
6. Availability of records to reliably evaluate type, frequency and treatment of bleeding episodes during at least 12 months preceding enrollment. Up to 24 months retrospective data should be collected if available. Availability of dosing and factor consumption during 12 months (up to 24 months) of treatment prior to enrollment is required for pdVWF switch subjects and is desired (but not a requirement) for on-demand subjects.
7. Subject is ≥18 years old at the time of screening and has a body mass index ≥ 17.5 but <40 kg/m^2.
8. If female of childbearing potential, subject presents with a negative blood/urine pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.[i]
9. Subject is willing and able to comply with the requirements of the protocol.

[i] Refer to Section 20.4 for a list of adequate contraceptive methods for females of childbearing potential.

9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

1. The subject has been diagnosed with Type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD (eg qualitative and quantitative platelet disorders or prothrombin time (PT)/international normalized ratio [INR] >1.4).
2. The subject is currently receiving prophylactic treatment with more than 5 infusions per week.
3. The subject is currently receiving prophylactic treatment with a weekly dose exceeding 240 IU/kg.
4. The subject has a history or presence of a VWF inhibitor at screening.
5. The subject has a history or presence of a FVIII inhibitor with a titer ≥0.4 Bethesda units (BU) (by Nijmegen modified Bethesda assay) or ≥0.6 BU (by Bethesda assay).
6. The subject has a known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins.
7. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
8. The subject has a medical history of a thromboembolic event.
9. The subject is human immunodeficiency virus (HIV) positive with an absolute Helper T cell (CD4) count <200/mm^3.
10. The subject has been diagnosed with significant liver disease per investigator's medical assessment of the subject's current condition or medical history or as evidenced by any of the following: serum alanine aminotransferase (ALT) greater than 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).
11. The subject has been diagnosed with renal disease, with a serum creatinine (CR) level ≥2.5 mg/dL.
12. The subject has a platelet count <100,000/mL at screening.
13. The subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to signing the informed consent.

14. The subject is pregnant or lactating at the time of enrollment.
15. Patient has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
16. The subject has participated in another clinical study involving another IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
17. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
18. The subject is scheduled for a surgical intervention.
19. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
20. The subject has a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
21. The subject is in prison or compulsory detention by regulatory and/or juridical order.
22. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.

9.3 Delay Criteria

1. If the subject has an acute bleeding episode or presents with an acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) the screening visit will be postponed until the subject has recovered.

9.4 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (i.e., reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the termination visit (including cases of withdrawal or discontinuation) are described in Section 10.6 and Section 20.2.

Discontinuation (i.e., complete withdrawal from study participation) may be due to dropout (i.e., active discontinuation by subject) or loss to follow-up (i.e., discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also will be withdrawn from treatment or discontinued from further study participation for the following reasons:

1. The subject is scheduled for an extended treatment period >3 months with non-topical immunomodulating drugs other than anti-retroviral chemotherapy (e.g., α-interferon, corticosteroid agents [equivalent to hydrocortisone greater than 10 mg/day]) during the course of the study.
2. Subjects with chronic hepatitis B or C develop ALT/AST levels exceeding 5 times the ULN for >1 month.
3. Subjects who experience severe hypersensitivity reactions, e.g., anaphylaxis upon exposure to rVWF (vonicog alfa).
4. Subjects who develop a neutralizing inhibitor to rVWF (vonicog alfa) and/or ADVATE (rFVIII, octocog alfa) (biological assays) that results in significant clinical effect, including but not limited to increasing the weekly dose of rVWF by ≥ 50%.
5. Subjects who demonstrate clinical signs of thromboembolic events.
6. The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through completion of the pregnancy and up to 1 year post delivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome.
7. The subject begins lactating. IP exposure will be discontinued. The investigator will record a narrative description of the course of the baby's development.
8. The subject is not compliant with the prophylactic treatment regimen and does not adhere to the frequency of IP administration. Once >30% of infusions are missed within a visit interval (3 months), the subject will be discontinued from further participation in the study.
9. The subject repeatedly uses other VWF products for prophylaxis or for the treatment of bleeding episodes in the absence of an acceptable justification to the sponsor.

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient who provides informed consent (i.e., signs and dates the informed consent form) is considered a subject enrolled in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (e.g., 071301) to be provided by the sponsor, 2- or 3-digit number study site number (e.g., 02) to be provided by the sponsor, and 3- or 4-digit subject number (e.g., 0003) reflecting the order of enrollment (i.e., signing the informed consent form). For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 071301-020003. All study documents (e.g., CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The study site is responsible for maintaining a screening log that includes all subjects who provided informed consent. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRF, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

The overall study design is illustrated in the Figure 1. Details on the procedures to be performed at each study visit, including screening, are provided in Supplement 20.2 "Schedule of Study Procedures and Assessments" and Supplement 20.3 "Clinical Laboratory Assessments".

10.3.1 Screening Visit

Written informed consent must be obtained from each subject before any study related procedures are performed. To initiate screening procedures, at least 72 hours must have elapsed since the last VWF administration for on-demand subjects and the subject must not be actively bleeding at the time of screening. For switch subjects, the usual interval between their pdVWF prophy infusions must have elapsed since the last VWF administration and the subject must not be actively bleeding at the time of screening. Multimer analysis and VWD gene mutation analysis should be performed at screening if not available in the subject's medical history.

The screening visit will be delayed if the subjects presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like symptoms, inflammatory diseases) until the event has resolved. All screening procedures and confirmation of eligibility shall take place within 42 days prior to the first infusion of IP. If the IP is not infused within 42 days, all screening assessments except blood group, human leukocyte antigen (HLA), genetics, multimeric pattern and [redacted], must be repeated to reconfirm eligibility. Refer to Supplement 20.2 and Supplement 20.3. Upon completion of screening procedures, subject eligibility will be confirmed by the sponsor on a subject eligibility form before additional study procedures are undertaken. The subject will maintain a diary that will include infusion logs (see Section 10.5). The allocation of IP will be initiated after the subject has qualified for home treatment (see Section 8.6.4.3.2).

In the event of a subject experiencing a bleeding episode that requires treatment between the screening visit and the subsequent visit (i.e. initial PK assessment visit for on-demand subjects or prophylaxis initiation visit for switch subjects), the subject will be treated with rVWF (vonicog alfa). If rVWF (vonicog alfa) is not available for any reason, e.g., subject not yet trained on IP administration, study site visit for IP administration not feasible, etc., the subject may use his/her standard of care, such as commercial pdVWF/FVIII products, and the reason for the use of non-IP products should be clearly documented.

10.3.2 Baseline Visit – Initial PK Assessment (On-demand Subjects Only)

After screening and confirmation of eligibility on-demand subjects will undergo an initial PK assessment. Subjects will receive a dose of 50 ± 5 IU/kg rVWF:RCo to determine VWF and FVIII levels. 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). See Section 20.2 and Section 20.3. IP infusion vials from the same lot number should be used for all PK-assessments per subject. Samples for measurement of FVIII and VWF activity taken through to 6 hours post-infusion will be obtained from an extremity different from that used for the infusion of IP. Where needed, the phlebotomy site will be kept patent via an infusion of normal saline. In this event, at least 5 mL of blood will be collected and discarded before collection of the next test sample into a fresh syringe.

If the subject has a central venous catheter, the central line should be used to administer the infusion and a peripheral venipuncture should be used to collect the blood samples.

In the event that a blood sample must be drawn through the central line used for administration of IP, the line must first be flushed with at least 10 mL normal saline or other suitable catheter flush solution that does not contain anticoagulant. At least 5 mL of whole blood must be collected and discarded prior to obtaining the sample.

If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.6.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment.

For pdVWF switch subjects, PK profile will not be assessed until reaching steady state after initiation of prophylaxis (see Section 10.3.4).

10.3.3 Prophylaxis Initiation Visit

The prophylaxis initiation visit will occur after the blood sample for the 96 hour PK assessment is drawn for on-demand subjects or within 42 days after screening and confirmation of eligibility for pdVWF switch subjects. The subject will receive the first rVWF (vonicog alfa) prophylactic dose of rVWF: RCo. Details on dose are provided in Section 8.6.4.3.

Procedures and assessments at this visit include (but are not limited to): AEs, bleeding episodes, medications taken, and non-drug therapies. Within 2 hours prior the IP infusion, a physical examination will be performed. Vital signs will be assessed within 30 minutes prior to IP rVWF (vonicog alfa) infusion and 30 minutes ± 15 minutes after IP infusion. Further details are provided in Supplement 20.2 and Supplement 20.3.

10.3.4 Initial Steady State PK-Assessment (pdVWF switch subjects only)

For pdVWF switch subjects, a full PK profile will be assessed at steady state conditions on two occasions. The initial PK assessment will be performed shortly after reaching steady state after starting prophylaxis dosing, which is suggested after 11 days post the 1st, around prophylaxis dose #5-6. The 2nd PK assessment at steady state will be performed at the end of the study.

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). In case the dosing schedule does not permit the 96 hr sampling, this sampling time point can be omitted (See Section 11.6). IP infusion vials from the same lot number should be used for all PK-assessments per subject.

Samples for measurement of FVIII and VWF activity taken through to 6 hours post-infusion will be obtained from an extremity different from that used for the infusion of IP. Where needed, the phlebotomy site will be kept patent via an infusion of normal saline. In this event, at least 5 mL of blood will be collected and discarded before collection of the next test sample into a fresh syringe.

If the subject has a central venous catheter, the central line should be used to administer the infusion and a peripheral venipuncture should be used to collect the blood samples. In the event that a blood sample must be drawn through the central line used for administration of IP, the line must first be flushed with at least 10 mL normal saline or other suitable catheter flush solution that does not contain anticoagulant. At least 5 mL of whole blood must be collected and discarded prior to obtaining the sample.

If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.6.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment. In case of surgery or bleeding, the PK assessment should be performed after 11 days after 1st prophylactic dose after re-start of prophylactic regimen. See section 11.6 for more details.

10.3.5 Treatment of Bleeding Episodes

Treatment of bleeding episodes is described in detail in Section 8.6.4.4 and treatment of perioperative bleeding is described in detail in Section 8.6.4.5.

10.3.6 Perioperative Visits (only applicable if surgery is needed)

The perioperative visits from priming dose through postoperative day 14 will be required to check daily intra- and postoperative weight-adjusted dose of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa). Details on the procedures and assessments performed at each visit can be found in Supplement tables in Section 20.2.1 and Section 20.3.1.

10.3.7 Follow-Up Visits (1 Month ± 1 Week, 2 Months ± 1 Week, 3 Months ± 2 Weeks, 6 Months ± 2 Weeks, 9 Months ± 2 Weeks post Prophylaxis Initiation Visit)

Visits will be performed after the prophylaxis initiation visit at 1 month ± 1 week, 2 months ± 1 week, and 3 months ± 2 weeks and thereafter every three months ± 2 weeks. Additional visits may occur if clinically indicated (see Section 10.3.8).

When possible, site visits should be scheduled on days when the subject is expected to infuse rVWF (vonicog alfa). Within 2 hours prior to the rVWF (vonicog alfa) IP infusion, a physical examination will be performed. Vital signs will be assessed within 30 minutes prior to IP infusion and 30 minutes ± 15 minutes after IP infusion. Incremental recovery (IR) will be determined at each follow-up visit based on VWF:RCo activity assessed prior to and after IP infusion.

The blood sample for IR analysis will be drawn within 30 minutes prior to IP infusion and 30 minutes ± 5 minutes after IP infusion. rVWF (vonicog alfa) will be infused at the regular prophylactic dose. For each subject's recovery analysis IP infusion, vials from the same lot number should be used.

Testing for VWF:RCo VWF:CB, rVWF:Ag, and FVIII:C level will be performed using the blood sample obtained before and after IP infusion.

The blood sample prior to IP infusion will also be used for the assessment of neutralizing and binding antibodies, clinical chemistry and hematology. For on-demand subjects, a washout period of at least 72 hours after the last infusion applies before the blood draw for the immunogenicity assays. For switch subjects, the wash out period may be reduced to the time interval between their pdVWF prophy infusions Bleeding episodes and the hemostatic efficacy will be evaluated based on the review of the patient diary. See Section 20.2 and Section 20.3. The evaluation of IP consumption and treatment compliance will be performed based on subject's diary entries. If a subject is not compliant with the prophylactic treatment regimen and does not adhere to the required frequency of administration of IP infusions (>30% of infusions were missed within a visit interval [3 months]) the subject will be withdrawn from the study.

At the 6 months ± 2 week visit an ECG will be performed and [redacted] data will be collected.

For the hemostatic efficacy assessment the following information will be recorded by the subject in the patient diary: bleeding location, type, severity, onset and resolution date and time, infusion date and time, clinical efficacy according to the rating scale. If at any time during the study a subject's bleeding episode does not adequately respond to rVWF (vonicog alfa) therapy, he/she will be evaluated for the presence of neutralizing and total binding antibodies. Refer to Section 12.9.3.2.

Further guidance on completing the subject's diary will be provided to the subjects during training for home treatment (see Section 8.6.4.3.2).

10.3.8 Unscheduled Visits

For any unscheduled visit (except for collection of IP) a clinical assessment will be performed as per the scheduled follow-up visits with the exception of [redacted], ECG, and IR determination (refer to Supplement 20.2 and Supplement 20.3).

Subjects who have more than one bleeding episode in 3 months, or an increased frequency of bleeding, should go to the study site for an unscheduled visit.

Follow-up visits after the subject has experienced a bleed may be requested by the investigator. Additional assessments may be required which are at the discretion of the investigator.

10.3.9 End of Study PK Assessment and Study Termination Visit (12 Months ± 2 Weeks post Prophylaxis Initiation Visit)

At the 12 month ± 2 week visit, a full PK analysis at steady state will be performed for both cohorts: on-demand and switch subjects. 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) unless dosing schedule does not permit, in which case the 96 hr sampling can be omitted. If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.6.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment and the PK assessment should be performed after 11 days after 1st prophylactic dose after re-start of prophylactic regimen. See Section 11.6 for more details.

Refer to Supplement 20.2 and Supplement 20.3 for the other assessments to be performed at the PK assessment and study completion visits.

For on-demand subjects, a washout period of at least 72 hours is required between the PK infusion and the study termination visit (at the time of the 96 hour postinfusion PK assessment). For switch subjects, the wash out period may be reduced to the time interval between their rVWF (vonicog alfa) prophy infusions.Refer to Supplement 20.2 and Supplement 20.3 for the list of assessments to be performed at the termination visit.

Subjects will be offered the option to continue to receive rVWF (vonicog alfa) in a long-term continuation study.

10.4 Medications and Non-Drug Therapies

The following medications and non-drug therapies are **not** permitted within 30 days before study entry and during the course of the study:

Medications:

- 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) and an extended treatment period >3 months.
- Another investigational and/or interventional study drug (except rVWF and FVIII administered under the surgery protocol).

A subject who has taken any of these medications or received any of these non-drug therapies during the study will be withdrawn from the study.

The following medications are permitted during the course of the study:

- Antifibrinolytics (e.g., tranexamic acid, ε-amino caproic acid) or topical hemostats as needed, according to each institution's standard of care. These may be used, in accordance with local standard clinical practice, as the initial or only treatment for minor and moderate bleeding events. However, if the bleeding has not stopped within 24 hour following administration of this non-VWF treatment, infusion(s) with rVWF (vonicog alfa) should be started per protocol
- Emergent use of a VWF concentrate other than rVWF (vonicog alfa) may be permissible under certain circumstances (see Section 8.6.4.4.1)

Details of all adjunctive hemostatic medication used, including dose and reason for use, must be recorded in the eCRF.

10.5 Subject Diary

1. An electronic subject diary will be provided to each subject at the screening visit to record the following information:
    - IP infusions to include date, start and stop times of the infusion, number of vials utilized, and infusion volume for prophylactic treatment or treatment of spontaneous and traumatic bleeding episodes
2. Details of bleeding episodes (site, type, severity and date/time of bleeding) and response to treatment as described in Section 8.6.4.4
3. Subjective hemostatic efficacy assessments

4. Untoward events/unwanted experiences
5. Concomitant medications (including immunizations) and non-drug therapies
6. Patient Reported Outcomes (PROs)

Subjects and/or their legally authorized representatives will be trained on use of the diary. The diary will be provided in electronic format and remain with the subject for the duration of the study. The investigator will review the diary for completeness and request missing information periodically and in a timely manner. The investigator will record/capture any unwanted experience reported by the subject which may qualify as an AE on the AE eCRF.

Infusions performed at the study site will first be recorded in the site's source documents and not in the patient diary.

Subject entries in the diary will serve as source records. During study participation the investigator has access to the database holding the subject diary data. After study closure, the investigator will receive the diary records for their subjects, including audit trail records, in PDF format. The data will be transmitted to the CRF by a validated transfer.

Paper diary may be utilized in rare case where electronic diary use is not possible.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have completed all study procedures according with the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, AE (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, e.g., technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the study termination visit. If the termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the termination visit.

If a subject terminates participation in the study and does not return for termination visit, his/her last recorded assessments shall remain with the last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.2 Schedule of Study Procedures and Assessments and Supplement 20.3 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

10.7 Procedures for Monitoring Subject Compliance

Subject compliance with the procedures of this study (treatment regimens and study visits) will be monitored by the investigator or a licensed healthcare professional at the study site.

During the regular scheduled follow-up visits a direct review of the subject's source data (e-diaries) will be performed at the sites and evaluated against the protocol requirements. In addition drug accountability will be evaluated at each follow-up study visit and the study termination visit by comparing the infusions recorded in the subject diary with empty vials returned by each subject to the study site, and the study site's dispensing record. Protocol deviations will be noted in the final report.

11. ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

11.1 Assessment of Spontaneous Bleeding Episodes/Annualized Bleed Rate

The annualized bleed rate (ABR) will be assessed based upon each individual spontaneous bleed, requiring coagulation factor replacement therapy, i.e., rVWF (vonicog alfa) treatment. The following details on bleeding episodes will be recorded by the subject in the electronic diary (for home treatment), the subject's healthcare provider in the site's source documents (for treatments away from the primary investigative site), or by authorized, qualified personnel at the participating site in the subject's medical records (for hospital-based treatment):

- Location of bleed; i.e., joint, menorrhagia, epistaxis, gastrointestinal, soft tissue, muscle, body cavity, intracranial, etc.
- Type of bleed; i.e., spontaneous, traumatic, unknown
- Severity of bleed; i.e., minor, moderate, and major (see Table 3)
- Date and time of onset of bleed
- Date and time of each infusion of rVWF (vonicog alfa) or rVWF (vonicog alfa)-ADVATE (rFVIII, octocog alfa) used to treat a bleeding episode
- Date and time of resolution of the bleeding episode

Study site personnel are qualified after they have undergone training during the qualification of the site.

All types of bleeds, including traumatic bleeds, will be recorded. Bleeding episodes should be organized by where they occur in addition to whether they occurred spontaneously or due to a traumatic event.

Bleeds occurring at the same anatomical location (e.g., right knee) with the same etiology (i.e., spontaneous versus injury) within 24 hours after onset of the first bleed will be considered a single bleed. Bleeding occurring at multiple locations related to the same injury (e.g., knee and ankle bleeds following a fall) will be counted as a single bleeding episode.

All efforts should be made to use rVWF (vonicog alfa) for treatment of bleeding episodes. If needed, the use of a VWF concentrate other than IP for the treatment of bleeding episodes will not disqualify the subject from further participation in the study.

11.2 Evaluation of ABR Before rVWF Prophylaxis and ABR Under rVWF Prophylactic Treatment

At screening, the subject's medical history will be recorded, including the number and location of all spontaneous and traumatic bleeding episodes within the past 12 months (up to 24 months if available). The maximum interval of bleed-free periods as well as trauma induced bleeding episodes will also be recorded (prospectively and retrospectively).

11.3 Number of Infusions and Total Weight Adjusted Consumption of rVWF and ADVATE and historical prophylaxis dosing and factor consumption during pdVWF prophylaxis treatment prior to enrollment

The number of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) (in case of bleeding episode treatment) infusions will be logged in the subject diary. Based on these entries the weight adjusted consumption will be calculated.

At the screening, historical pdVWF dosage and dosing frequency during 12 and up to 24 months of pdVWF prophylactic treatment prior to enrollment will be recorded for the pdVWF switch subjects in order to calculate the consumption of pdVWF.

11.4 Assessment of Efficacy for Treatment of Bleeding Episode

Investigators will be asked to assess and record hemostatic efficacy after resolution of each bleeding episode using the 4-scale rating system outlined in Table 4.

Table 4
Efficacy Rating Scale

Rating	Efficacy Rating Criterion	
	Minor and Moderate Bleeding Events	**Major Bleeding Events**
Excellent (=1)	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF containing coagulation factor containing product required	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF containing coagulation factor containing product required
Good (=2)	1-2 infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required	< 1.5 x infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required
Moderate (=3)	3 or more infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required	≥ 1.5 x infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required
None (=4)	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF containing coagulation factor containing product required	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF containing coagulation factor containing product required

11.5 Assessment of Efficacy for Treatment for Surgical Bleeding

For those undergoing surgery, the operating surgeon will be asked to assess and record actual versus predicated blood loss and intraoperative hemostatic efficacy immediately after surgery.

The investigator will be asked to assess and record an overall assessment of hemostatic efficacy 24 hours after the last perioperative rVWF (vonicog alfa) infusion or at day 14 post-operation, whichever occurs first, using the 4-scale rating system described in Table 5.

Table 5
Assessment of Hemostatic Efficacy

Rating	Overall Assessment of Hemostatic Efficacy 24 Hours After the Last Perioperative rVWF Infusion
Excellent (1)	Intra- and post-operative hemostasis achieved with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) was as good or better than that expected for the type of surgical procedure performed in a hemostatically normal subject
Good (2)	Intra- and post-operative hemostasis achieved with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) was probably as good as that expected for the type of surgical procedure performed in a hemostatically normal subject
Moderate (3)	Intra- and post-operative hemostasis with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) was clearly less than optimal for the type of procedure performed but was maintained without the need to change the rVWF (vonicog alfa) concentrate
None (4)	Subject experienced uncontrolled bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of rVWF (vonicog alfa) concentrate

11.6 rVWF Pharmacokinetics and Pharmacodynamics

PK will be assessed twice for all subjects.

For on-demand subjects, an initial PK assessment using a dose of 50 IU ± 5 IU/kg rVWF:RCo will be performed at the baseline visit, and 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 week 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 assay. 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 assessment using the subject's individualized dose will be performed shortly after reaching steady state, which is estimated to be reached for the majority of subjects after approximately 11 days from the 1st prophylactic dose. To fit any logistical requirements, samples for PK analysis can be taken after prophylaxis dose #5-6, and whenever possible, sample collections should be during the longer partial interval of the alternating irregular dosing intervals. For example, if a subject follows a dosing regimen as follows:

Date	Weekday	Dose number	Interval	Time from 1st 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 profile will be assessed at the end of the study, i.e. 12 month ± 2 week visit with a PK 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 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). If the dosing interval for a certain switch subject wouldn't allow for the full 11 post-infusion timepoints sample collection, 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 for an individual switch subject.

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

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

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, whether or not considered causally related to the IP.

12.1.1.1 Serious Adverse Event

An SAE is defined as an untoward medical occurrence that, at any dose, meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are (including but not limited to):
  - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse

- Reviewed and confirmed seroconversion for HIV, hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)
- Development of clinically significant neutralizing VWF antibodies
- Development of neutralizing antibodies to FVIII (titer ≥0.4 BU [by Nijmegen- modified Bethesda assay] or ≥0.6 BU [by Bethesda assay])
- Thromboembolic events (e.g., myocardial infarction, stroke, transient ischemic attack [TIA], deep vein thrombosis [DVT] or pulmonary embolism)
- Hypersensitivity reactions (e.g., anaphylaxis [for definition, refer to Section 12.6.2] and other immediate and delayed hypersensitivity reactions which may manifest with urticarial rash, pruritus, flushing, angioedema of the face, extremities, or laryngeal tissues [leading to throat tightness with stridor], wheezing, gastrointestinal symptoms, and/or hypotension)

Uncomplicated pregnancies, following maternal or paternal exposure to IP are not considered an AE/SAE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE and should be reported per SAE reporting guidelines provided in Section 12.1.2.3 (Safety Reporting).

12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any suspected adverse reaction to study treatment that is both serious and unexpected is considered a SUSAR.

The event(s) must meet all of the following:

- Suspected adverse reaction (which implies that there is reasonable evidence indicating a causal relationship between the event and the study treatment),
- Unexpected (per Reference Safety Information (RSI)/IB), and
- Serious

Once determined to meet the criteria for a SUSAR, the sponsor will ensure expedited SUSAR reporting is completed in line with the regulatory requirements in participating countries as outlined in the Safety Management Plan.

12.1.1.3 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet any of the seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) listed in Section 12.1.1.1.

12.1.1.4 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (e.g., IB, PI [prescribing information]). "Unexpected" also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.1.1.5 Preexisting Disease

Preexisting diseases that are present before entry in to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described as "worsening" of the pre-existing condition on the AE CRF.

12.1.2 Assessment of Adverse Events

For the purposes of this study, the following will not be considered as AEs and will not be included in the analysis of AEs.

- Bleeding episodes are part of the underlying disease and therefore are not AEs; they will be evaluated in the context of efficacy.
  - For non-serious bleeding episodes caused by an injury, the injury would not be reported as an AE, unless it resulted in a medical finding other than a bleeding episode (e.g., abrasion of skin). Therefore, any VWD-related bleeding event (e.g., epistaxis, gastrointestinal bleeding, musculo-skeletal bleeding, menorrhagia) that is non-serious will not be reported as an AE. However, the investigator may decide that the event is an AE if the event also would have occurred in a healthy individual under the same circumstances.

  - For serious bleeding episodes (bleeding SAEs): Bleeding events that meet seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) should be captured on the SAE eCRF and reported as an SAE to the Sponsor or designee (e.g., CRO) on an SAE Report form as described in Section 12.1.2.3 (Safety Reporting).

- Seroconversion after documented HAV/HBV vaccination prior to or during the study period.

Each AE from the first IP exposure to the study completion date will be described on the AE CRF using the term representing medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial verbatim expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2

For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable, action taken with regards to the study treatment (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution or until the subject's condition returns to the level at the baseline for pre-existing conditions.

If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the protocol-specified dosage (including underdosing /overdosing [<20 IU/kg rVWF:RCo or >100 rVWF:RCo], abuse, and withdrawal, treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions,

and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after administration of IP will be reported on a Pregnancy Form and followed-up at 1 year post-delivery, if feasible.

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the SAE Form within 24 hours after awareness: no additional reporting on CRFs is necessary.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, e.g., assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP, is not biologically plausible per mechanism of action of the IP, or has a much more likely alternative etiology).
- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of IP
  - An alternative etiology is equally or less likely compared to the potential relationship to the IP
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
    - Reappearance of a similar reaction upon re-administration (positive re-challenge)
    - Positive results in a drug sensitivity test (skin test, etc.)
    - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
  - Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within 5 days after IP infusion, the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

12.1.2.3 Safety Reporting

AEs and SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Section 20.2) and Section 12.1.2.

Adverse Events and SAEs are to be recorded on the AE page of the eCRF. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the IP, must be reported immediately (within 24 hours of the study center's first knowledge of the event). All SAEs must be reported in English via the Electronic Data Capture (EDC) system by completing the relevant eCRF page(s) and also by SAE Report Form via fax/email to Sponsor's Global Drug Safety (Baxalta GDS) department within 24 hours of becoming aware of the event for SAEs (for contacts, instructions, and additional details, refer to the SAER form).

Within 24 hours of site awareness of a SAE (or Pregnancy) study sites will complete and send all SAE (or Pregnancy) reports to a dedicated:

Baxalta Global Drug Safety fax number: [redacted]

OR

email: [redacted]

The responsible Site Monitor will review the SAE (or Pregnancy) Reports for completeness, will reconcile the reports against the EDC database, and will follow-up with sites to obtain missing information and/or information requiring clarification. Any SAE associated with a pregnancy must be reported on the SAER Form.

For Follow-up Reports, the site shall use a new SAER form (marked as Follow-up) and the new information should be entered together with a brief narrative identifying the updated data.

An SAER should include the following minimum information:

1. Protocol Number (on all pages)
2. Subject identification number (on all pages) and demographics (gender, age at onset of event and/or date of birth)
3. Investigational product and treatment regimen (including date of the first dose of IP, date of the last dose of IP prior to the onset of the SAE)
4. Medical Term for Event (Diagnosis preferably)
5. Description of the SAE, including:
    - Date of onset
    - Causal relationship assessment by the Investigator
6. Seriousness criteria (e.g., death, life-threatening, hospitalization, medically significant, or other criterion)
7. Name, address, fax number, email, and telephone number of the reporter/Investigator

Post-trial SAE Reporting: In compliance to EudraLex Volume 10 (Clinical trials guidelines, Chapter II: Safety Reporting from the European Commission), which references an EMA guidance (ICH Topic E 2 A - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting), clinical sites/the investigator should report to the Sponsor SAEs after a subject´s study completion. Study sites will be provided a Post-Trial SAER form to complete and report these post-study SAEs to the Sponsor within the 24 hours of their awareness. Site Monitor will instruct the site that any such Post-Trial SAEs should be reported on the study-specific Post-Trial SAER form if/when the site becomes aware of it. Such information will not be actively monitored by the sponsor after completion of the study.

These events shall be reported to Baxalta GDS who will process them in the same way as SAEs occurring during the study. Post-Trial SAEs do not need to be captured in the study EDC database if it is already locked. Irrespective if captured in the EDC database or not, such Post-Trial SAEs will become part of the GDS database. The monitor should remind the clinical site about the post-trial SAE reporting requirements during interim monitoring visits, upon each subject's study completion as well as during the close-out visit.

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of the clinical trial
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor.
In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committees (ECs) and relevant competent authority(s) are notified of the urgent measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (i.e., from the time of signed informed consent up to but not including the first IP exposure) will be described on the SAER. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE.** NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g. reconstitution difficulty
- Missing components
- Damage to the product or unit carton

- A mislabeled product (e.g., potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) 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. The subject's medical history will also include documented history of on-demand or pdVWF prophylaxis treatment for at least the past 12 months and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 months (up to 24 months if available).

All medications taken and non-drug therapies received in the 2 weeks prior to study entry and all concomitant medications and non-drug therapies during study will be recorded on the CRFs.

Data on medical history, drug and non-drug therapy history of those subjects who transition from surgery rVWF (vonicog alfa) study will be used from the eCRF of the main studies, will be updated, if applicable, and transcribed into the respective eCRF of the prophy study.

12.6 Physical Examinations

At screening and subsequent study visits (as described in Section 10.3), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 12.1.1.5), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.6.1 Thromboembolic Events

There is a risk of occurrence of thrombotic events, particularly in patients with known clinical or laboratory risk factors for thrombosis including low ADAMTS13 levels. Therefore, patients at risk must be monitored for early signs of thrombosis during the study and prophylaxis measures against thromboembolism should be instituted according to current recommendations and standard of care. Additional diagnostic procedures are required according to each institution's standard of care which may consist of, but are not limited to the following:

- For DVT: Magnetic Resonance Imaging (MRI), compression ultrasound or impedance plethysmography.
- For pulmonary embolism: ECG, chest radiography, perfusion/scintiscan or MRI.
- For myocardial infarction: ECG, cardiac enzymes, echocardiography
- For stroke: diffusion-weighted magnetic resonance imaging or computed tomography, ABCD scoring, carotid imaging

Results of diagnostic procedures may be forwarded to the sponsor to be reviewed by an independent external expert panel, such as the DMC, if applicable.

12.6.2 Anaphylaxis

The diagnosis of anaphylaxis is highly likely when any of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g, generalized urticaria, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
    b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a. Involvement of the skin or mucosal tissue (e.g., generalized urticaria, pruritus or flushing, swollen lips-tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

c. Reduced BP or associated symptoms (hypotonia [collapse], syncope, incontinence)

d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to a known allergen for that patient (minutes to several hours):

a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP

b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP

If a subject develops anaphylaxis in the course of the clinical study, this needs to be reported as SAE (Section 12.1.1.1). Additional blood will be drawn for Anti-VWF IgE antibody testing (Section 12.9.13).

12.7 Vital Signs

Vital signs will be assessed pre- and post-infusion at each visit, if not stated otherwise:

- Height (cm) (Screening only) and weight (kg) (pre-infusion only)
- Blood pressure: Systolic/diastolic blood pressure (mmHg) baseline measurements will be measured after a 10-minute rest in the supine/semi-recumbent position.
- Pulse rate: Pulse rate (beats/min) will be measured at the distal radial arteries under the same conditions as above.
- Respiratory rate: Respiratory rate (breaths/min) will be measured over a period of 1 minute under the same conditions as above.
- Temperature: Body temperature ($^{\circ}$C or $^{\circ}$F) may be determined by oral, rectal, axillary, or tympanic measurement at the discretion of the investigator. However, the same method should be used for all measurements in 1 subject.

Vital signs (pulse rate, respiratory rate, and blood pressure) should be recorded within 30 min before and after IP administration. The assessment of vital signs per planned study visit is outlined in Supplement 20.2.

Vital sign values are to be recorded on the physical examination eCRF. For each vital sign value, the investigator will determine whether the value is considered an AE (see definition in Section 12.1). If assessed as an AE, the medical diagnosis (preferably), symptom, or sign, will be recorded on the AE eCRF.

Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE, should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.8 Electrocardiogram

A standard 12-lead ECG at rest will be performed at screening, at the 6 month follow-up visit and at the study termination visit and evaluated for medical significance by the investigator.

12.9 Clinical Laboratory Parameters

Refer to the Laboratory Manual for information on collection and processing of samples.

In general all laboratory tests will be performed at central laboratories, except the pregnancy and blood group test which will be performed at the local laboratory. In addition, relevant critical safety laboratory tests for complete blood count (CBC), serum chemistry and/or coagulation parameters such as VWF and FVIII activity may also be performed in the local laboratory to ensure that results will be available immediately to the investigator. In principle, results from the central laboratory will be used for data analysis purposes. The assays performed in the central laboratories are specified in the Laboratory Manual. The investigator will supply the sponsor with a list of the normal ranges and units of measurement for the laboratory variables to be determined at the site. Laboratory values such as antibodies to other proteins are not required immediately and will be assessed later during the course of the study.

Any abnormal laboratory value that is considered clinically significant by the investigator based on a local laboratory test result (reference range and the units to be provided) should be confirmed by a central laboratory test result for which the sample is drawn/collected within 24 hours of the abnormal finding by the local laboratory.

12.9.1 rVWF Pharmacokinetics and Pharmacodynamics

Details on pharmacokinetic and pharmacodynamics assessments are provided in Section 11.6.

12.9.2 Hematology and Clinical Chemistry

The hematology panel will consist of CBC [hemoglobin, hematocrit, erythrocytes (ie, red blood cell count [RBC]; mean corpuscular volume [MCV], mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration [MCHC]), and leukocytes (i.e., white blood cell count [WBC])] with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.

The clinical chemistry panel will consist of sodium (Na), potassium (K), chloride (Cl), ALT, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase (AP), blood urea nitrogen (BUN), CR, and glucose (Glu).

Blood will be obtained for assessment of hematology and clinical chemistry parameters at screening, during PK-assessment prior to rVWF (vonicog alfa) IP infusion, after 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours post rVWF (vonicog alfa) IP infusion, at all follow-up visits as per schedule (refer to Supplement 20.3 Clinical Laboratory Assessments), i.e., 4 weeks ± 1 week, 8 weeks ± 1 week and every 3 months ± 2 weeks, and at study completion. Hematology and clinical chemistry assessments will be performed on Ethylenediaminetetraacetic acid (EDTA)-anticoagulated whole blood and serum, respectively, at the central laboratory.

12.9.3 Immunology

12.9.3.1 Antibodies to VWF and FVIII

All subjects will be tested for binding and neutralizing antibodies to VWF and FVIII at screening, at initial PK assessment, at each of the scheduled follow-up visits and at the study completion visit. Testing will be done prior to IP infusion and with at least a 72 hour wash out period since the last IP infusion. If there is any suspicion of inhibitor development (e.g. excessive bleeding) binding and neutralizing antibodies to VWF and FVIII may be tested at the discretion of the investigator.

12.9.3.2 Neutralizing and Total Binding Anti-VWF Antibodies

The assays to establish the presence of neutralizing and total binding anti-VWF antibodies have been established in the absence of international standards and with only limited numbers of positive controls. Therefore, caution is advised in interpreting positive results. In particular, any clinical association, changes in the natural history of the disease, effect of therapy, etc. needs to be taken into account for final judgment. The sponsor's Medical Director should be consulted for additional advice. As part of the AE follow-up, any sample testing positive needs to be confirmed after 2-4 weeks for central laboratory testing. Only confirmed neutralizing anti -VWF antibodies are considered inhibitors (see Section 12.9.3.4). These subjects need to be closely monitored and therapy adjusted accordingly.

12.9.3.3 Binding antibodies to VWF

The presence of total binding anti-VWF antibodies will be determined by an enzyme-linked immunosorbent assay (ELISA) employing polyclonal anti-human Immunoglobulin (Ig) antibodies (IgG, IgM and IgA). For this assay (ELISA), recombinant human VWF will be coated onto a microtiter plate, then incubated with dilutions of the positive control, the negative control or test sample. Antibodies against human VWF that are present in the samples bind to the coated antigen and will be detected with a horseradish peroxidase (HRP)-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a human monoclonal antibody specific for human VWF spiked into the negative control. The negative control for this assay is pooled normal human plasma.

Plasma samples are analyzed for binding antibodies against the specific antigen in two steps. First, the sample is screened for antibodies and the titer of binding antibodies is determined. Second, the specificity of positive antibody results is confirmed.[16]
In brief, all samples are serially diluted (initial dilution 1:20 and further diluted 1:2).

The titer endpoint, defined as the highest dilution that still gives a positive signal above cut off level, is determined in two independent duplicates. The cut off level is established based on background signal level of healthy plasma donors (n=160) and set to include 5% false positives to be as sensitive as possible (95% percentile). The ELISA assay is validated allowing an assay variability of ± 1 titer step. Therefore, differences ≤ 2 titers steps may be due to variability of the ELISA assay. Specificity has to be confirmed in a competition assay when a sample has a titer of 1:80 or higher in the screening assay. Based on the validation criteria samples tested in the screening assay at 1:20 or 1:40 cannot be confirmed in the competition assay. A positive screening value is confirmed if the difference between the titers determined for the subject sample (re-screen) and for the subject sample with pre-incubation (confirmation sample) is > 2 titer steps. Antibody titers of subject samples will only be reported as positive, if the results of the screening and confirmatory analysis fulfill these acceptance criteria. The titer to be reported is always the one determined in the original screening procedure (independent of the result of the re-screening in the confirmation procedure).

A more detailed test procedure will be supplied upon request or pro-actively if a sample tests positive. A treatment related increase of the binding anti-VWF antibodies is expected, if the titer increases by more than 2 titration steps. These subjects need to be closely monitored and therapy adjusted accordingly.

12.9.3.4 Neutralizing Antibodies to VWF

Three functional VWF assays, VWF:CB, VWF:RCo and VWF:FVIIIB assays, will be used to test for the presence of neutralizing anti-VWF antibodies. Neutralizing antibodies to VWF:RCo, VWF:CB and VWF:FVIIIB activities will be measured by assays based on the Bethesda assay established for quantitative analysis of FVIII inhibitors (Nijmegen modification of the Bethesda assay).[17] The amount of inhibitor is expressed as BU per mL. One BU is thereby defined as the amount of inhibitor that decreases the measured activity in the assays to 50% of that of the negative control samples. The assays were validated using human plasma samples from two type 3 VWD patients with low (1-2 BU/mL) and high (~10 BU/mL) titer inhibitors and plasma samples from non-human primates immunized with human rVWF (vonicog alfa) (>100 BU/mL).

If a subject has a measurable baseline level of VWF activity in the respective assay, it is taken into account in the calculation of the residual activity. However, if baseline levels are too high (>15% VWF:RCo), inhibitors may not be reliably detected.

To exclude false positive results, the detection limit for anti-VWF inhibitors was set to 1 BU/ml for all 3 assays. The rationale for this cut-off value is the relatively high CI of the underlying assays, making determinations at the end of the evaluation range of the Bethesda reference curve uncertain.[18] A more detailed test procedure may be requested to further characterize the anti-VWF inhibitors, if detected.

Only confirmed positive anti-VWF inhibitor test result will be reported and will be considered as a medically significant SAE.

12.9.3.5 Binding Antibodies to FVIII

Binding antibodies against FVIII will be analyzed using a proprietary enzyme immunoassay. The testing strategy will be as described for binding anti-VWF antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.3.6 Neutralizing Antibodies (Inhibitors) to FVIII

Neutralizing antibodies (inhibitors) to FVIII will be assessed by the Nijmegen modification of the Bethesda assay in a central laboratory. To verify a FVIII inhibitor, additional testing (such as tests for Lupus anticoagulants) may be initiated. Positive FVIII inhibitor tests will be defined as ≥ 0.4 BU by the Nijmegen-modified Bethesda assay that is confirmed by a second test performed on an independent sample obtained 2-4 weeks following the first test. Only confirmed positive FVIII inhibitor test result will be reported.

12.9.4 Antibodies to Other Proteins

Plasma will be assayed for the presence of antibodies against CHO protein (total Ig), murine IgG and human Furin (total Ig) using proprietary enzyme immunoassays. The testing strategy will be as described for binding anti- VWF antibodies.
Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.4.1 Anti-CHO Protein

Total Ig antibodies (IgG, IgA, IgM) against CHO protein will be analyzed. For this assay (ELISA), CHO protein derived from cultures of untransfected cells and propagated under the identical cell culture conditions used for ADVATE (rFVIII, octocog alfa) production will be coated onto a microtiter plate, then incubated with dilutions of the positive control, negative control or test sample. Antibodies against CHO protein that are present in the samples bind to the coated antigen and will be detected with a HRP-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a polyclonal goat anti-CHO protein antibody spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.4.2 Anti-Murine IgG

A commercially available ELISA (Medac, Hamburg, Germany) will be used to detect and to quantify IgG antibodies originating from human plasma that are directed against mouse-IgG (HAMA: human anti- mouse antibodies). Microtiter plates coated with mouse IgG will be incubated with dilutions of the standard, the positive control, the negative control or the test sample. Antibodies against mouse IgG that are present in the samples bind to the coated antigen and form a bridge to a peroxidase coupled mouse IgG antibody that will be used for detection (bridging format of the ELISA assay).
The positive control for this assay will be a polyclonal goat anti-murine IgG spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.4.3 Antibodies to Human Furin

Total Ig antibodies (IgG, IgA, IgM) against human Furin will be analyzed. For this assay (ELISA), recombinant human Furin will be coated onto a microtiter plate, then incubated with dilutions of the positive control, the negative control or test sample. Antibodies against human Furin that are present in the samples bind to the coated antigen and will be detected with a HRP-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a human monoclonal antibody specific for human Furin spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.5 Viral Serology

The following viral seromarkers will be assessed at screening:

- HIV: anti-HIV 1, HIV 2
- HAV: anti-HAV (IgG and immunoglobulin M [IgM])
- HBV: Hepatitis B surface antigen (HbsAg), anti-Hepatitis B (HB) core, anti-HBs
- HCV: anti-HCV ELISA
- Parvovirus B19: anti-B19V (IgG and IgM)

Virus serology will be established during the screening period. The relevant confirmatory Polymerase Chain Reaction (PCR) testing may be performed from appropriate left-over samples as needed.

12.9.6 Urinalysis (Dipstick)

The urinalysis will include assessments for erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite and pH and will be performed at the central laboratory.

12.9.7 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. The pregnancy test may need to be repeated during the course of study in countries where mandated by national law.

12.9.8 VWD Mutational Analysis, Multimer Analysis and Human Leukocyte Antigen Genotyping

A cell pellet (buffy coat and erythrocytes) will be retained at the screening visit for VWD gene mutational analysis, VWF multimer analysis and HLA genotype determination if the information is not already available in the subject's medical history. Results from multimer analysis (see Section 12.9.10.1) may contribute to VWD gene mutational analysis. The genetic testing will be done, when the subject consents to the genetic testing.

12.9.9 Blood Group Analysis

The blood group needs to be determined during the screening period. If the information is not already available in the subject's medical history, it has to be determined at the local lab.

12.9.10 Additional Laboratory Testing in Case of Thromboembolic Events

rVWF (vonicog alfa) contains ULMW multimers because of a lack of exposure to endogenous VWF protease (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) during the manufacturing process. In vitro and in vivo cleavage of these ultralarge molecular fractions by ADAMTS13 and generation of characteristic satellite bands has been extensively demonstrated during nonclinical and clinical development. Nevertheless, the potential elevated risk of thrombosis and/or other thromboembolic complications due to the administration of ultra large molecular VWF multimers in subjects with normal levels of VWF cannot be completely excluded. Therefore VWF multimer analysis will not only be performed routinely at screening but in case of thromboembolic events, both VWF multimer analysis as well as ADAMTS13 activity will be determined to assess any relatedness of these occurrences with IP treatment.

12.9.10.1 VWF Multimer Analysis

The VWF multimer pattern will be assessed using low-resolution sodium dodecyl sulfate (SDS)–agarose gel electrophoresis. High-resolution SDS–agarose gel electrophoresis, with agarose concentrations >1.5%, will be used to determine the satellite band structure of VWF. These analyses will employ Western blot with luminescence video imaging.

12.9.10.2 ADAMTS13 Activity

VWF73 was identified as the 73 amino acid minimal region of the VWF A2 domain required for ADAMTS13 cleavage. The cleavage of this substrate will be detected by a commercially available ELISA-based Chromogenic assay (Technoclone Austria): Cleavage of immobilized VWF73 substrate is detected by a HRP-labeled antibody directed against the cleavage site of VWF73. The amount of bound antibody, which is the function of the ADAMTS13 cleavage is detected by a chromogenic substrate.

12.9.11 Soluble P-Selectin (sP-Selectin)

sP-selectin is a cell adhesion molecule (CAM) found in granules in endothelial cells (cells lining blood vessels) and activated platelets. Data for an association between the sP-selectin concentration, TTP and venous thromboembolism (VTE) are limited and the predictive value has not yet established. A commercial ELISA assay will be employed as an exploratory test. sP-selectin will be determined at the Screening visit and used as indicator for an increased thrombotic risk.

12.9.12 D-Dimer

D-dimer will be used as a marker for DVT and disseminated intravascular coagulation (DIC). While a negative result practically rules out thrombosis, a positive result can indicate thrombosis but does not rule out other potential etiologies, including a recent hemorrhage. Its main use, therefore, is to exclude thromboembolic disease where the probability is low. D-Dimer will be measured at the Screening visit and used as indicator for an increased thrombotic risk.

12.9.13 Additional Laboratory Testing in Case of Severe Hypersensitivity Reactions

If a subject develops a severe hypersensitivity reaction in the course of the clinical study, additional blood will be drawn for anti-VWF IgE antibody testing. The presence of anti-VWF IgE will be determined by using the ImmunoCAP®, a VWF-specific IgE blood test (Thermo Scientific). The basis of the ImmunoCAP® technology is a cellulose polymer as solid phase in a plastic capsule providing a large surface for protein binding. rVWF (vonicog alfa) as antigen is covalently coupled to the cellulose polymer.

Detection of specific anti-VWF IgE bound to the antigen will be accomplished by a secondary enzyme-labeled anti-human IgE antibody. Testing for binding anti-human VWF IgE antibodies will be done with 0.5 mL plasma. Antibody containing samples will be identified and quantified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.14 Assessment of Laboratory Values

12.9.14.1 Assessment of Abnormal Laboratory Values

For VWF and FVIII laboratory assessments no evaluation of clinical significance is necessary.

Each other laboratory value (except results to determine genetics of the underlying VWD disease and blood group) has to be assessed by the investigator and the assessment will be recorded on the eCRF. The investigator will determine for each abnormal laboratory value whether the value is considered clinically significant or not and provide the reference range including the units. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 12.1) and record the sign, symptom, or medical diagnosis on the AE CRF, is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.5), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, i.e. because it is due to a preexisting disease, due to a lab error, due to variation or due to another issue that will be specified.

Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator. Any abnormal laboratory value that is considered clinically significant by the investigator based on a local laboratory test result (reference range and the units to be provided) should be confirmed by a central laboratory test result for which the sample is drawn/collected within 24 hours of the abnormal finding by the local laboratory.

Any seroconversion result for HIV, HAV, hepatitis B virus (HBV), HCV, HEV, or B19V shall be re-tested.

12.10 [redacted]

12.10.1 [redacted]

12.10.2 [redacted]

[redacted]

13. STATISTICS

13.1 Sample Size and Power Calculations

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 cohort (OD and switch). A total of at least 5 type 3 VWD subjects will be followed for 12 months. 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).[1]

13.2 Datasets and Analysis Cohorts

13.2.1 Safety Analysis Set

The Safety Analysis Set will be composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

13.2.2 Full Analysis Dataset

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

13.2.3 Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set will be composed of subjects who are at least 70% compliant regarding the number of scheduled prophylactic infusions (as measured by the ratio of actual number of infusions to planned number of infusions). Only subjects who met all study entry criteria and who had no major protocol violations that might impact primary efficacy assessments will be included in the PP analysis set.

13.2.4 PK Full Analysis Set

The Pharmacokinetic Full Analysis Set (PKFAS) will be composed of all subjects who received the PK infusion and who provided acceptable data for PK and PD analysis. Acceptable PK/PD data will be defined in the Statistical Analysis Plan.

13.2.5 PK Per Protocol Analysis Set

The Pharmacokinetic 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 affecting the PK period of the study as defined in the detailed Statistical Analysis Plan.

13.3 Handling of Missing, Unused, and Spurious Data

13.3.1 General

Statistical techniques will not be used to identify and exclude any observations as outliers from the analyses. If data are considered spurious, e.g. for lack of biological plausibility, it will be documented to include the reason for exclusion and the analyses from which the data were excluded.

13.3.2 Other

1. Regarding missing data in PK records:
    - Body weight: If a subject's weight is missing from the PK infusion record, the subject's last recorded weight will be used to calculate the weight-adjusted dose.
    - Concentration:
        - Baseline concentration levels reported as below the limit of quantification will be considered to be 0. Missing VWF baseline concentration levels (VWF: RCo, VWF: AG or VWF: CB) for Type 3 subjects will be set to 0.
    - Time:
        - If start time of infusion is missing (but stop time is available) and actual collection time is available, then stop time of infusion will be taken for further calculation (i.e. time difference between actual end date/time of infusion and date/time blood sample drawn).
        - If actual collection date/time is missing and planned collection date/time is missing, then this PK time point will be taken out from the PK analysis (i.e. no data entry for this time point).
        - For all other scenarios, the planned collection date/time will be taken for further calculation.
2. Regarding missing data in AE records:
    - Handling of unknown causality assessment:
        - If a subject experiences an AE with a missing causality assessment, the relationship of the AE will be counted as "related."

- Handling of unknown severity grades:
  - If a subject experiences more than one AE categorized under the same preferred term, 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.

13.4 Methods of Analysis

The study success criteria are the objectives as stated in Section 7. “Treatment success” was defined as the extent of control of bleeding episodes achieved during this study.

13.4.1 Primary Outcome Measure

The primary outcome measure is ABR for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa). No formal statistical hypothesis test is planned for the analysis. The primary efficacy analysis will be based on the FAS and will be summarized by the two cohorts: on-demand and switch subjects. As a supportive analysis, the same analysis will also be carried out on the PP analysis set.

The spontaneous ABR while treated with rVWF (vonicog alfa) for each cohort will be estimated using a negative binomial regression. The prior ABR will be based on historical data collected from each enrolled subject.

The two ABRs (prior to prophylaxis treatment and while on prophylaxis) for each cohort will be compared within each subject using a generalized linear mixed-effects model (GLMM) (with a logarithmic link function, the default for the negative binomial distribution), accounting for the fixed effect of the two treatments. The follow-up time (in years) will be specified as an offset. The ratio of ABR while in the study to historical ABR will be estimated and reported together with the 95% confidence interval for each of the two cohorts.

The difference in on-study ABR relative to historical ABR will be also summarized descriptively.

13.4.2 Secondary Outcome Measures

In general, data for secondary efficacy analysis will be summarized by the two cohorts: on-demand and switch subjects and when applicable overall. Mean, standard deviation, median, range, quartiles will be calculated for continuous endpoints. Proportions, will be calculated for categorical endpoints. Confidence intervals at the two-sided 95% level will be provided when appropriate.

13.4.2.1 Additional Efficacy of Prophylaxis Treatment with rVWF

The number and proportion of on-demand subjects with ABR percent reduction success (i.e.≥ 25%) will be calculated together with a two-sided, 95% CI for the proportion.

The number and proportion of pdVWF switch subjects ABR preservation success will be reported together with the corresponding 95% two-sided CIs for the proportion.

The number and proportion of subjects with categorized spontaneous ABR (i.e. 0, 1-2, 3-5, more than 5 bleeds) will be reported descriptively.

Summary statistics for the total number of infusions, as well as average number of infusions per week will be provided. The total weight adjusted consumption of rVWF (vonicog alfa) during prophylactic treatment will be provided. If applicable, historical data on consumption of pdVWF prior to the study will be summarized as well.

The change in spontaneous ABR from the historical rate to that during the rVWF (vonicog alfa) prophylaxis period will be summarized by location of bleeding (GI, epistaxis, joint bleeding, menorrhagia, oral and other mucosa, muscle and soft tissue, etc.).

13.4.2.2 Pharmacokinetic and Pharmacodynamic Analysis

All PK and PD analyses will use the actual sampling times, not nominal times specified in the protocol, wherever possible. Actual sampling times will be defined as time from the start of infusion to the blood sample collection time. A deviation from the protocol-specified blood sample 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 results were biologically implausible will be eliminated from the analysis.

If any concentration data are considered spurious (e.g. lack of biological plausibility), the reason for exclusion from the analysis and the analysis from which the data point was excluded will be documented.

Details of calculation of PK and PD parameters and corresponding analysis will be given in the statistical analysis plan.

The following PK parameters, based on the initial PK assessment after a washout for on-demand subjects, will be listed and summarized descriptively for VWF:RCo, VWF:Ag and VWF:CB: IR, $T_{1/2}$, MRT, $AUC_{0-\infty}$, $AUC_{0-tlast}$, C_{max}, T_{max}, V_{ss}, and CL. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity, based on the initial PK assessment after a washout for on-demand subjects will be assessed using C_{max}, T_{max}, and $AUC_{0-tlast}$. These PD parameters will be listed and summarized descriptively. PK parameters at steady state ($AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$) for the partial dosing interval will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study for VWF:RCo, VWF:Ag and VWF:CB and summarized descriptively for subjects with the same dosing regimens. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity will be assessed using $AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$. These PD parameters will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study and will be summarized descriptively for subjects with the same dosing regimens.

For the on-demand subjects, the PK of VWF:RCo will be analyzed using a population PK approach to characterize the single and multiple dose pharmacokinetics, including associated variability assessed at after washout and at end of study, respectively. The population PK analysis will be performed in a stepwise manner as outlined below.

1. Exploratory graphical analysis of VWF:RCo versus time data for identification of potential outliers and to inform the pharmacometric analysis.
2. Population PK model development for rVWF (vonicog alfa):
    a. Evaluate alternative structural and stochastic models to describe the typical and individual rVWF (vonicog alfa) profiles.
    b. Investigate and characterize the potential for a time dependency in CL of rVWF (vonicog alfa).
    c. Evaluate, and if necessary refine, the candidate final model

Details of this Population PK analysis will be given in a separate Population PK analysis plan.

For the switch subjects, differences in $AUC_{0\text{-}tau;ss}$, $C_{max;ss}$, and $C_{min;ss}$ assessess shortly after reaching steady state and assessed at the end of the study will be assessed by the ratio of geometric means and corresponding two-sided 95% confidence intervals for VWF:RCo, VWF:Ag,VWF:CB, and FVIII:C. These analyses will be performed using a linear mixed effects model with PK assessment (i.e. factor of two levels relating to the PK assessment shortly after reaching steady state and the PK assessment at end of study, respectively) as a fixed effect and subject as a random effect based on log-transformed PK parameters. 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.

Descriptive statistics will be used to summarize VWF:RCo, VWF:AG and VWF:CB and FVIII:C levels for each nominal time point on the PK curve.

For all subjects in the PKFAS activity/concentration vs. time curves will be prepared.

Formulas for PK parameters IR, $T_{1/2}$, MRT, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}tlast}$, C_{max}, T_{max}, V_{ss}, and CL, $AUC_{0\text{-}tau;ss}$, $C_{max;ss}$, $T_{max;ss}$,and $C_{min;ss}$ will be given in the statistical analysis plan and will be derived using non-compartmental methods in WinNonlin. Analysis of these parameters will be carried out on the PKFAS as well as on the PKPPAS.

13.4.2.3 Safety

Safety analysis will be performed overall and by the two cohorts: on-demand and switch subjects.

TEAEs are defined as AEs with start dates on or after the first exposure to IP. Summaries of AEs will be based on TEAEs unless otherwise indicated.

Occurrence of AEs and SAEs will be summarized descriptively, by system organ class and preferred term. The number and percentage of subjects who experienced AEs and SAEs, and the number of AEs and SAEs will be tabulated. In addition, the number of subjects who experienced AEs assessed as related to IP by the investigator, and the number of IP-related AEs will be tabulated. The number of patients with AEs by severity will be presented similarly.

A listing of all AEs will be presented by subject identifier, age, sex, preferred term and 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.

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 infusion, irrespective of being related or not related to treatment. Temporally associated AEs will be presented in summary tables.

AEs that occurred before first IP infusion will be listed separately.

Adverse events of special interest (AESI), such as hypersensitivity reactions and thromboembolic events, will be monitored throughout the study and statistical analysis will be conducted based on the search criteria (eg, standardised MedDRA queries [SMQ]) determined prior to database lock, and summarized.

For immunogenicity, frequency counts and percentages will be calculated for 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. Clinically significant changes relative to baseline in vital signs and clinical laboratory parameters (hematology, clinical chemistry) will be reported.

13.4.3 Exploratory Outcome Measures

[redacted]

13.4.3.1 [redacted]

[redacted]

13.4.3.2 [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

13.4.3.3 [redacted]

[redacted]

13.4.3.4 [redacted]

[redacted]

13.5 Planned Interim Analysis of the Study

No formal interim analysis is planned for this study.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Trial Agreement (CTA). If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the CTA.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable national and local regulatory requirements as described in the CTA. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

15.1.1 Investigator Report and Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the CTA. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the CTA. Auditing processes specific to the study will be described in the audit plan.

15.5 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. Also, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing whenever pdVWF is used instead of rVWF (vonicog alfa). The reason for this use must also be provided to the sponsor. The sponsor (Baxalta) will also ensure the responsible EC and relevant competent authority are notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.6 Laboratory and Reader Standardization

A central laboratory/reader will be used for all clinical assessments except for pregnancy testing and blood group test (refer to Section 12.9). Local laboratories are requested to provide their laboratory specifications of the individual tests that are also being tested locally.

16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the CTA.

16.2 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the CTA.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

16.3 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients and/or their legally authorized representative must sign an informed consent form before entering into the study according to applicable national and local regulatory requirements and ICH GCP. Before use, the informed consent form will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 16.2). The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable national and local regulatory requirements. Patients or their legally-authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent form, patients or their legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised informed consent form, which have been approved by the applicable EC and regulatory authorities, will be provided by the investigator to the subjects who consented to participate in the study

16.4 Data Monitoring Committee

This study will be monitored by aDMC. The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. 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 stop a trial if it finds toxicities or if treatment is proven to be not beneficial. Details will be defined in the DMC charter.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the CTA.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.7), records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, CRFs, SAERs, laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

If electronic format CRFs are provided by the sponsor, only authorized study site personnel will record or change data on the CRFs. If data is not entered on the CRFs during the study visit the data will be recorded on paper and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (e.g., ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the CTA.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the CTA.

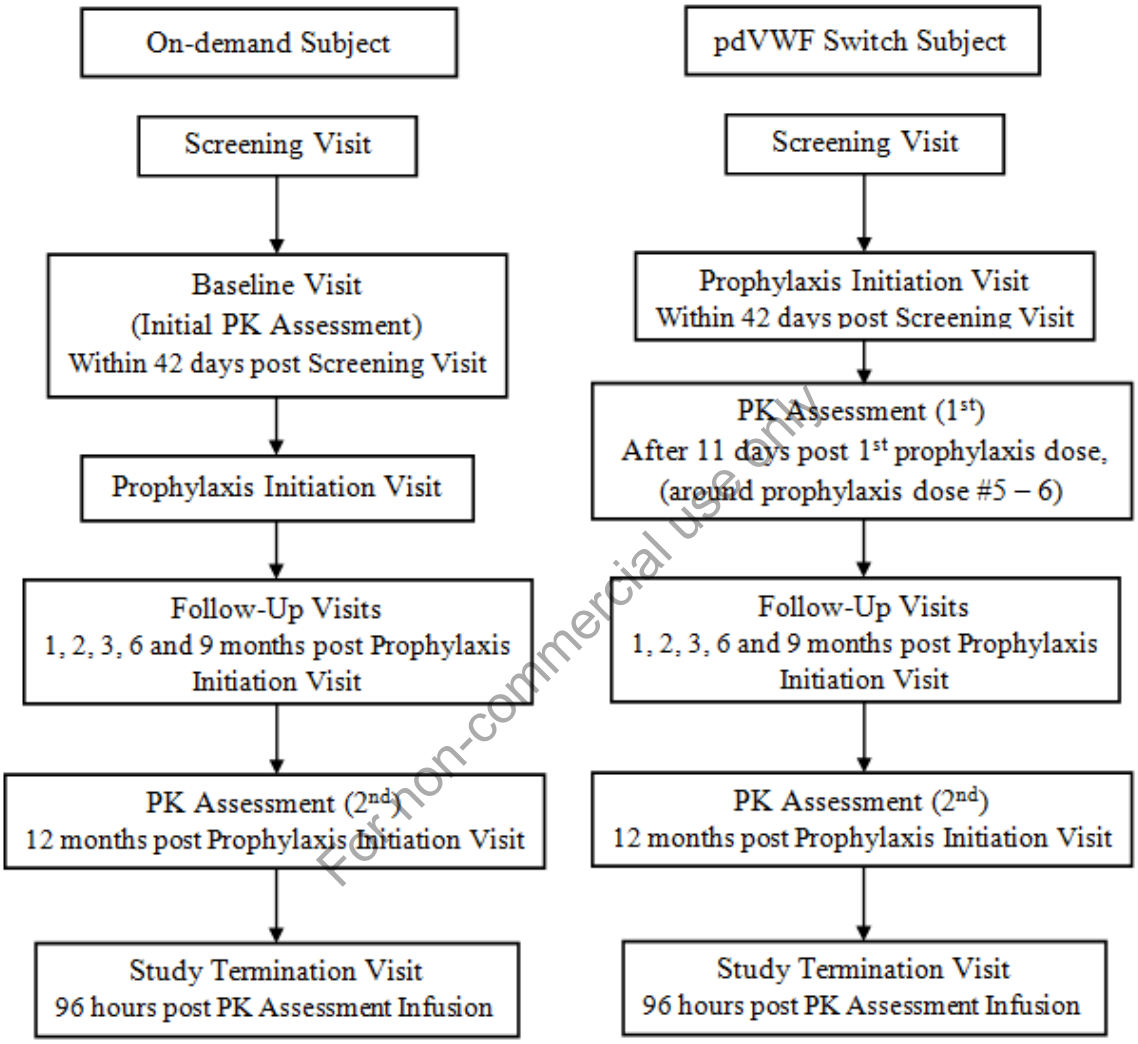
19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the CTA.

20. SUPPLEMENTS

20.1 Study Flow Chart

Figure 1
Study Design for Baxalta Clinical Study 071301



20.2 Schedule of Study Procedures and Assessments

Table 6a
Schedule of Study Procedures and Assessments for On-demand Subject

Procedures/ Assessments	Screening Visit	Baseline Visit (PK-assessment visit)			Prophylaxis Initiation Visit	Interval/Follow-Up Study Visits					PK Assessment at Study Completion			Termination Visit
		Pre-infusion[g]	Infusion	Post-infusion[g]		1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion[g]	Infusion	Post-infusion[g]	Conducted at the 96 hour postinfusion PK Assessment
											12 month ± 2 weeks			
Informed Consent[a]	X													
Eligibility Criteria	X													
Medical History[b]	X													
Concomitant Medications[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-drug Therapies[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X			X	X	X	X	X	X	X			X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Bleeding Episodes and Treatment and Hemostatic Efficacy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratories	X	X		X	X[h]	X	X	X	X	X	X		X	X
Vital Signs[d]	X	X		X	X	X	X	X	X	X	X		X	X
ECG	X								X					X
IP Treatment[e]			X		X	X	X	X	X	X		X		
IP Consumption / Treatment Compliance						X	X	X	X	X				
Subject Diary					X	X	X	X	X	X				
[redacted]	X[f]								X					X

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Continued

[a] Occurs at enrollment (before screening).
[b] Including documented history of on-demand treatment for the past 12 months (up to 24 months if available) and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 (up to 24) months.
[c] Including all medications and non- drug therapies taken in the 2 weeks prior to study entry and all the concomitant medications and non-drug therapies during the course of the study.
[d] Vital signs: height, weight, body temperature, pulse rate, respiratory rate, and blood pressure. Height is only required at the screening visit. The time points for pre- and post-infusion measurements are (weight is measured pre-infusion only): within 30 minutes before infusion start and 30 ± 15 minutes post-infusion.
[e] IP treatment after the prophylactic treatment initiation visit at the site will be continued as home-treatment if the subject qualifies; a wash-out period of at least 72 hours is required after the last IP infusion before the follow-up visit. IP infusion will be given at the study site after the blood sample for immunology testing and IR determination is drawn.
[f] Can be done either at the screening or the baseline visit.
[g] Time points for PK blood draws: 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 (the 96 hr sampling can be omitted if not allowed by the dosing interval).
[h] If a subject did not undergo PK assessment, laboratory assessments will be performed at this visit.

Table 6b
Schedule of Study Procedures and Assessments for pdVWF Switch Subject

Procedures/ Assessments	Screening Visit	Prophylaxis Initiation Visit	PK Assessment (at prophylaxis dose #5-6)			Interval/Follow-Up Study Visits					PK Assessment at Study Completion			Termination Visit
			Pre-infusion[g]	Infusion	Post-infusion[g]	1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion[g]	Infusion	Post-infusion[g]	Conducted at the 96 hour postinfusion PK Assessment
											12 month± 2 weeks			
Informed Consent[a]	X													
Eligibility Criteria	X													
Medical History[b]	X													
Concomitant Medications[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-drug Therapies[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X	X			X	X	X	X	X	X			X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Bleeding Episodes and Treatment and Hemostatic Efficacy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratories	X	X	X		X	X	X	X	X	X	X		X	X
Vital Signs[d]	X	X	X		X	X	X	X	X	X	X		X	X
ECG	X								X					X
IP Treatment[e]		X		X		X	X	X	X	X		X		
IP Consumption / Treatment Compliance						X	X	X	X	X				
Subject Diary		X				X	X	X	X	X				
[redacted]	X[f]								X					X

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Continued

[a] Occurs at enrollment (before screening).
[b] Including documented history of prophylaxis treatment for the past 12 months (up to 24 months if available) and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 (up to 24) months.
[c] Including all medications and non- drug therapies taken in the 2 weeks prior to study entry and all the concomitant medications and non-drug therapies during the course of the study.
[d] Vital signs: height, weight, body temperature, pulse rate, respiratory rate, and blood pressure. Height is only required at the screening visit. The time points for pre- and post-infusion measurements are (weight is measured pre-infusion only): within 30 minutes before infusion start and 30 ± 15 minutes post-infusion.
[e] IP treatment after the prophylactic treatment initiation visit at the site will be continued as home-treatment if the subject qualifies; a wash-out period of at least 72 hours is required after the last IP infusion before the follow-up visit. IP infusion will be given at the study site after the blood sample for immunology testing and IR determination is drawn.
[f] Can be done either at the screening or the prophylaxis initiation visit.
[g] Time points for PK blood draws: 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 (the 96 hr sampling can be omitted if not allowed by the dosing interval).

20.2.1 Summary Schedule of Visit Assesments for Surgical Bleeding

Table 7
Summary Schedule of Visit Assesments for Surgical Bleeding

Procedures/ Assessments	**Surgical procedure**				**Post-Operative Day 7 Visit (± 1 day)**	**Post-Operative Day 14 Visit (± 2 day)**
	Priming Dose Procedures (12-24 hours prior to surgery)	**Loading Dose Procedures (≤ 3 hours prior to surgery)**	**Intraoperative**	**Postoperative (day 1 → end of perioperative IP treatment)[a]**		
ECG						X
Physical examination[b]	X	X		X	X	X
Adverse events	X	X	X	X	X	X
Laboratories[c]	X	X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X
IP treatment: rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) or rVWF (vonicog alfa) only infusion	X	X	X as required	X as required	X as required	X as required
Concomitant medications and non-drug therapy	X	X	X	X	X	X
[redacted]						X
Hemostatic efficacy assessments[e]			X	X	X	X
Blood loss		X estimated	X actual	X	X[f]	X[f]
Treatment days estimate		X				

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[a] The assessments will be performed daily until perioperative IP treatment end (potentially multi-visits)
[b] Physical Examination: within 2 hours prior to IP infusion start
[c] For laboratory assessments, see Table 9
[d] Vital signs: within 30 minutes before infusion start and 30 ± 15 minutes post-infusion
[e] Completed immediately postsurgery by the operating surgeon 24 hours post last IP infusion or at Day 14 visit (whichever occurs first) by the investigator
[f] In case bleeding still ongoing

20.3 Clinical Laboratory Assessments

Table 8a
Clinical Laboratory Assessments for On-demand Subject

Procedures/ Assessments	Screening Visit	Baseline Visit (PK-assessment visit)			Prophylaxis Initiation Visit[k]	Interval/Follow-Up Study Visits					PK Assessment[m] at Study Completion			Termination Visit
		Pre-infusion	Infusion	Post-infusion		1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion	Infusion	Post-infusion	Conducted at the 96 hour postinfusion PK Assessment
											12 month± 2 weeks			
Hematology[a]	X	X		X	X	X	X	X	X	X	X		X	X
Clinical Chemistry[b]	X	X		X	X	X	X	X	X	X	X		X	X
Coagulation Panel/ PK assessment[c]	X	X		X	X	X	X	X	X	X	X		X	
Immunogenicity[d]	X	X			X[l]	X	X	X	X	X	X			X
Viral Serology[e]	X													
Urinalysis[f]	X													
VWD Gene Mutational Analysis / HLA genotype analysis and Analysis of VWF multimers[g]	X													
sP-selectin and D-dimer	X[h]													
Blood Group[i]	X													
Pregnancy Test[j]	X													

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[a] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. Hematology assessments during PK assessments will be determined prior to IP infusion and 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours thereafter. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

[b] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin. Clinical chemistry will be determined prior to IP infusion and after 24 ± 2 h, 48 ± 2 hours and 72 ± 2 hours during the PK assessments. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

[c] Coagulation panel/PK assessment (also refers to IR pre/post dose assessments at prophy initiation visit and each follow-up visit): PT, INR and aPTT (only for screening), VWF:RCo, VWF:Ag, VWF:CB, FVIII:C,; during the PK assessment at the baseline visit blood samples will be drawn 30 min prior PK infusion; once the PK infusion is completed 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 and VWF:RCo, VWF:CB, VWF:Ag, FVIII:C will be determined; for follow-up visits, IR samples will be drawn within 30 minutes pre-infusion and 30 ± 5 minutes post-infusion. During screening and in case of thromboembolic event VWF multimers and ADAMTS13 will be analyzed to judge on a possibly relatedness to UHMW fractions of the IP.

[d] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII –Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG . In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined. For on-demand subjects, a washout period of at least 72 hours after the last IP infusion is required before blood samples for immunogenicity assessments can be drawn.

[e] Viral Serology 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; HIV-1/HIV-2 Antibodies

[f] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH

[g] Not required if available in the subject's medical history; VWF multimers: additionally in case of thromboembolic events

[h] At screening and in case of thromboembolic events

[i] Blood group assessment major blood group (local laboratory) only if not available in the subject's medical history

[j] Serum pregnancy test (in females of child-bearing potential if no urine sample is available)

[k] The last post-infusion laboratory assessments coincide with the initiation visit for prophylactic treatment. After the blood samples are drawn for laboratory assessment for the 96 h post infusion PK assessment, the subject receives the first IP infusion for prophylactic treatment (prophylactic treatment initiation visit).

[l] Only needed for subjects without PK assessment prior to their first IP infusion in this study.

[m] A steady state full PK analysis will be performed at the end of the study. 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), the 96 hr sampling can be omitted if not allowed by the dosinig interval.

Table 8b
Clinical Laboratory Assessments for pdVWF Switch Subject

Procedures/ Assessments	Screening Visit	Prophylaxis Initiation Visit	PK Assessment[k] (at prophylaxis dose #5-6)			Interval/Follow-Up Study Visits					PK Assessment[k] at Study Completion			Termination Visit
			Pre-infusion	Infusion	Post-infusion	1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion	Infusion	Post-infusion	Conducted at the 96 hour postinfusion PK Assessment
											12 month± 2 weeks			
Hematology[a]	X	X	X		X	X	X	X	X	X	X		X	X
Clinical Chemistry[b]	X	X	X		X	X	X	X	X	X	X		X	X
Coagulation Panel/PK assessment[c]	X	X	X		X	X	X	X	X	X	X		X	
Immunogenicity[d]	X	X				X	X	X	X	X	X			X
Viral Serology[e]	X													
Urinalysis[f]	X													
VWD Gene Mutational Analysis / HLA genotype analysis and Analysis of VWF multimers[g]	X													
sP-selectin and D-dimer	X[h]													
Blood Group[i]	X													
Pregnancy Test[j]	X													

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[a] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. Hematology assessments during PK assessments will be determined prior to IP infusion and 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours thereafter. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

[b] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin. Clinical chemistry will be determined prior to IP infusion and after 24 ± 2 h, 48 ± 2 hours and 72 ± 2 hours during the PK assessments. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

[c] Coagulation panel/PK assessment (also refers to IR pre/post dose assessments at prophy initiation visit and each follow-up visit): PT, INR and aPTT (only for screening), VWF:RCo, VWF:Ag, VWF:CB, FVIII:C,; during the PK assessment blood samples will be drawn 30 min prior PK infusion; once the PK infusion is completed 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 and VWF:RCo, VWF:CB, VWF:Ag, FVIII:C will be determined; for follow-up visits, IR samples will be drawn within 30 minutes pre-infusion and 30 ± 5 minutes post-infusion. During screening and in case of thromboembolic event VWF multimers and ADAMTS13 will be analyzed to judge on a possibly relatedness to UHMW fractions of the IP.

[d] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII – Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG. In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined. For switch subjects, the wash out period may be reduced to the time interval between their pdVWF prophy infusions.

[e] Viral Serology 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; HIV-1/HIV-2 Antibodies

[f] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH

[g] Not required if available in the subject's medical history; VWF multimers: additionally in case of thromboembolic events

[h] At screening and in case of thromboembolic events

[i] Blood group assessment major blood group (local laboratory) only if not available in the subject's medical history

[j] Serum pregnancy test (in females of child-bearing potential if no urine sample is available)

[k] A full steady state PK analysis will be performed. 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) , the 96 hr sampling can be omitted if not allowed by the dosinig interval.

20.3.1 Laboratory Sampling for Surgical Bleeding

Table 9
Laboratory Sampling[a] for Surgical Bleeding

Procedures/ Assessments	**Surgical procedure**				**Post-Operative Day 7 Visit (± 1 day)**	**Post-Operative Day 14 Visit (± 2 day)**
	Priming Dose Procedures (12-24 hours prior to surgery)	**Loading Dose Procedures (≤ 3 hours prior to surgery)**	**Intraoperative**	**Postoperative (day 1 → end of perioperative IP treatment)[b]**		
Hematology[c]	X (w/o Differential)	X[d] (w/o Differential)		X (w/o Differential)	X	X
Clinical Chemistry[e]	X	X[d]			X	X
Coagulation panel[f]	X	X	X	X	X	X
VWF inhibitory and binding antibodies, antibodies to other proteins[g]	X	X	X if excessive or unexplained bleeding	X	X	X
Urinalysis[h]					X	X
VWF Multimers[i]						
Anti VWF IgE antibody testing only in case of allergic reaction/ anaphylaxis						

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[a] Blood draws are within 3 hrs prior to infusion start, expect that for the priming dose blood draw is within 30 minutes prior to infusion start. For coagulation panel, an additional 30 ± 5 minutes post-infusion blood draw is needed.
[b] The assessments will be performed daily until perioperative IP treatment end (potentially multi-visits)
[c] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.
[d] Not required if sample already drawn at the time of the priming dose
[e] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin.
[f] Coagulation panel: VWF:RCo, VWF:Ag, FVIII:C PT INR and aPTT; in additiona to pre-infusion, 30 ± 5 minutes post infusion blood draw is needed.
[g] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII – Neutralizing and Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG. In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined.
[h] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH
[i] VWD multimers and ADAMTS13 during the study only in case of thrombotic events

20.4 Contraceptive Methods for Female Subjects of Childbearing Potential

In this study, subjects who are women of childbearing potential must agree to utilize a highly effective contraceptive measure throughout the course of the study and for 30 days after the last administration ofIP. In accordance with the Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials (version 2014-09-15)[ii], birth control methods which may be considered as highly effective include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable[iii]
- Intrauterine device (IUD)[iii]
- Intrauterine hormone-releasing system (IUS) [iii]
- Bilateral tubal occlusion[iii]
- Vasectomised partner(s)[iii]
- Sexual abstinence during the entire study period

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

[ii] Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf.

[iii] Contraception methods that are considered to have low user dependency.

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19. [redacted]

20. [redacted]

21. [redacted]

22. SUMMARY OF CHANGES

Protocol 071301: Local Amendment 8 (Czech Republic): 2018 MAY 18

Replaces: Local Amendment 5 (Czech Republic): 2017 AUG 08

In this section, changes from the previous local version of the protocol, dated 2017 AUG 08, are described and their rationale is given.

1. Throughout the document
   Description of Change:
   Minor grammatical and/or administrative changes and/or rewording have been made.
   Purpose for Change: To improve the readability and/or clarity of the protocol.

2. Throughout the document
   Description of Change:
   INN was added to rVWF and ADVATE by changing rVWF to rVWF (vonicog alfa) and changing ADVATE to ADVATE (rFVIII, octocog alfa).
   Purpose for Change: To add INN.

3. Section 2, Section 12.1.2
   Description of Change:
   Bleeding events that meet seriousness criteria should be reported on both SAE eCRF and SAE report form. Section 12.1.2.3 was added as a reference for SAE assessment.
   Purpose for Change: To provide further clarifications on SAE reporting.

4. Synopsis (Clinical condition(s)/indication(s)), Section 6.4, Section 13.1
   Description of Change:
   Original text:
   Subjects with severe von Willebrand disease (VWD) requiring prophylactic treatment with coagulation factor replacement.
   New text:
   Subjects with severe von Willebrand disease (VWD) **(baseline VWF:RCo <20 IU/dL)** requiring prophylactic treatment with coagulation factor replacement.
   Purpose for Change: To add definition of severe VWD.

5. Synopsis (Planned study period), Section 8.2
   Description of Change:
   The initiation/completion and duration of the study were updated per the new timeline.
   Purpose for Change: To reflect the new study timeline.

6. Synopsis (Study purpose, Study design), Section 7.1, Section 8.1
   Description of Change:
   Hypersensitivity was added for safety evaluation; PK and pharmacoecnomics evaluation was added.
   Purpose for Change: To provide further clarifications to the purpose of the study.

7. Synopsis (Primary objective), Section 7.2
   Description of Change:
   Original text:
   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 and to compare it to the subject's historical ABR **for spontaneous bleeding episodes during on-demand treatment**.
   New text:
   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 and to compare it to the subject's historical ABR for spontaneous bleeding episodes.
   Purpose for Change: To remove wording to accommodate pdVWF switch subject cohort, which is a new study cohort added in this amendment.

8. Synopsis (Secondary objectives), Section 7.3
   Description of Change:
   [redacted] Additional wording was added to clarify the objectives.
   Purpose for Change: Remove some of the objectives ([redacted]) and add clarification.

9. Synopsis (Exploratory objectives, Exploratory outcome measures), Section 7.4, Section 8.3.3
   Description of Change:
   [redacted] and additional wording was added to clarify the assessments.
   Purpose for Change: Clarification and adding additional objectives/assessments.

10. Synopsis (Study Design), Section 8.1
    Description of Change:
    Additional details about the study design were added for on-demand and the switch cohort.
    Purpose for Change: To provide further clarification and to add study design for the switch cohort.

11. Synopsis (Primary outcome measure), Section 8.3.1
    Description of Change:
    Original text:
    Prospectively recorded ABR for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF **and the subjects' historical ABR for spontaneous bleeding episodes during on-demand treatment**.
    New text:
    Annualized bleeding rate (ABR) for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa).
    Purpose for Change: To remove the unnecessary text.

12. Synopsis (Secondary outcome measures), Section 8.3.2
    Description of Change:
    Rewording some of the exisiting secondary outcome measures (efficacy and safety) to provide clarification. New efficacy outcome measures were added to further access the efficacy of prophylaxis for switch subjects. Clinically significant changes in vital signs and clinical laboratory parameters were added as one additional safety measure. New steady-state PK parameters were added. PD parameters were added. [redacted]
    Purpose for Change: To provide further clarifications and to add new outcome measures for switch subjects. And to remove some of the outcome measures ([redacted])

13. Synopsis (Investigational product(s), dose and mode of administration)
    Description of Change:
    Prophylaxis dosing guidelines were added for the pdVWF switch subjects.
    Purpose for Change: To add dosing guide for the switch subjects.

14. Synopsis (Targeted accrual, sample size calculation), Section 6.4, Section 13.1
    Description of Change:
    Sample size was increased and targeted accrual of each cohort was added and a followup period of 12 months was added.
    Purpose for Change: To update the sample to reflect the adding of switch cohort.

15. Synopsis (Inclusion criteria, Exclusion criteria), Section 9.1, Section 9.2
    Description of Change:
    Criteria for the switch subjects were added.
    Criteria added to clarify no pre-planned surgery is allowed.
    Purpose for Change: To update for the eligibility of switch subjects and to add some clarity.

16. Synopsis (Inclusion Criteria), Section 9.1
    Description of Change:
    Original text:
    Subject is ≥18 years old at the time of screening and has a body mass index ≥18 but <30 kg/m^2.
    New text:
    Subject is ≥18 years old at the time of screening and has a body mass index ≥~~18~~**17.5** but <~~30~~**40** kg/m^2.
    Purpose for Change: To update the BMI value from "18-30" range to "17.5-40" range, in response to query received from regulatory authority in Czech Republic only.

17. Synopsis (Planned statistical analysis), Section 13.4
    Description of Change:
    Changes were made throughout the section according to the updated outcome measures. Remove the planned analysis of exploratory outcome measure from synopsis to avoid redundance
    Purpose for Change: To better test the updated outcome measures.

18. Section 5
    Description of Change:
    New abbreviations were added.
    Purpose for Change: Clarification.

19. Section 6.5, Section 6.5.2, Section 6.5.2.4, Section 6.5.2.5
    Description of Change:
    Summary of recently completed clinical study 071101 was added as Section 6.5.2.4, the summary of 071401 was moved to Section 6.5.2.5 .
    Purpose for Change: To provide clinical study summary for study 071101.

20. Section 6.5.2.3
    Description of Change:
    To add wording about the basis of the dosing for the current study.
    Purpose for Change: To provide clarification.

21. Section 6.6
    Description of Change:
    Original text:
    He/she may benefit from a product that minimizes excessive FVIII administration.
    New text:
    He/she may benefit from a product that minimizes excessive FVIII administration **and thus allowing individualized dosing of VWF at optimal levels**.
    Original text:
    By using a recombinant product, the risk of **contamination with blood derived viruses or variant Creutzfeldt-Jakob Disease** associated with the use of products of human or animal origin has been **virtually** eliminated.
    New text:
    By using a recombinant product, the risk of **transmission of adventitious agents and other blood-borne pathogens** associated with the use of products of human or animal origin has been eliminated.
    Purpose for Change: To provide accuracy and clarification.

22. Section 6.6
    Description of Change:
    Original text:
    These benefits outweigh the following potential risks of rVWF.
    New text:
    These benefits outweigh the following **identified or** potential risks of rVWF
    Purpose for Change: To provide accuracy since thromboembolic events has been upgraded to identified risk.

23. Section 8.5
    Description of Change:
    Updates were made based on safety considerations.
    Purpose for Change: To avoid unnecessary study stop.

24. Section 8.6.3
    Description of Change:
    Wording was added to clarify that partial vials are not allowed to use.
    Wording about mixing of two products was removed as it is not allowed any more.
    Purpose for Change: To provide clarification on IP administration.

25. Section 8.6.4.1
    Description of Change:
    Details about PK assessment IP treatment were added for both on-demand and switch cohorts.
    Purpose for Change: To provide more details and clarifications.

26. Section 8.6.4.2
    Description of Change:
    Prophylaxis initiation treatment was updated to be also applicable to the switch subjects and the dosing details were removed from this section (moved to Section 8.6.4.3).
    Purpose for Change: To provide details to accommodate newly added switch cohort.

27. Section 8.6.4.3, Section 8.6.4.3.1, Section 8.6.4.3.2
    Description of Change:
    Detailed instructions of prophylaxis dosing and dosing adjustment were added to this section for both on-demand and pdVWF switch subjects. Home treatment rules were also made applicable to switch subjects, and made correction that the investigator is responsible for the home treatment procedures.
    Purpose for Change: To provide details and clarifications to accommodate newly added switch cohort.

28. Section 8.6.4.4.1, Section 10.3.1
    Description of Change:
    Added the requirement of documentation the reason for the use of any non-IP product or therapy.
    Purpose for Change: To ensure proper documentation of non-IP product use.

29. Section 8.6.4.4.2
    Description of Change:
    Added the wording about dose adjustment and the optional use of ADVATE.
    Purpose for Change: To provide further clarification.

30. Section 8.6.4.5
    Description of Change:
    Sentence was added to clarify no pre-planned surgery is allowed.
    Purpose for Change: To add some clarity.

31. Section 8.6.4.5.2
    Description of Change:
    Added description of priming dose for surgery.
    Purpose for Change: To provide further clarification.

32. Section 8.6.4.5.3
    Description of Change:
    Added description of loading dose for surgery.
    Purpose for Change: To provide further clarification.

33. Section 8.6.4.6, Section 12.6.1
    Description of Change:
    Added the details about prophylaxis measures against thromboembolism.
    Purpose for Change: To ensure safety monitoring of thromboembolic events.

34. Section 8.6.5
    Description of Change:
    Added the wording about the requirement to monitor temperature excursions at the subject's home.
    Purpose for Change: To ensure IP is stored as specified in the Pharmacy Manual.

35. Section 9.4
    Description of Change:
    Original text:
    Subjects who develop a neutralizing inhibitor to rVWF and/or ADVATE (biological assays).
    New text:
    Subjects who develop a neutralizing inhibitor to rVWF and/or ADVATE (biological assays) **that results in significant clinical effect, including but not limited to increasing the weekly dose of rVWF by ≥ 50%.**
    Purpose for Change: To provide more clarifications.

36. Section 9.4
    Description of Change:
    One more discontinuation criteria was added.
    Purpose for Change: To avoid the continue of non-compliance subjects.

37. Section 10.3.1
    Description of Change:
    Added the wording to clarify the wash-out period of the screening visit and the timing of the subsequent visit for switch subjects.
    Purpose for Change: To clarify for switch subjects.

38. Section 10.3.2
    Description of Change:
    Wording was added to specify this visit only applicable to on-demand cohort.
    Purpose for Change: To provide clarification.

39. Section 10.3.3
    Description of Change:
    Wording was added to specify the timing of this visit for the switch cohort.
    Purpose for Change: To provide clarification.

40. Section 10.3.4
    Description of Change:
    The initial steady-state PK assessment that only applicable to the switch subjects was specified in this section.
    Purpose for Change: To accommodate PK assessment of switch subjects.

41. Section 10.3.5, Section 10.3.6, Section 10.3.7, Section 10.3.8, Section 10.3.9
    Description of Change:
    The original Sections from 10.3.4 – 10.3.8 became 10.3.5 – 10.3.9 due to the insertion of new Section 10.3.4.
    Purpose for Change: To accommodate the insertion of new Section 10.3.4.

42. Section 10.3.7
    Description of Change:
    The value of prophylaxis dose was removed since it was not correct for switch patients. The different wash-out period for switch subjects was specified.
    Purpose for Change: To make corrections and to make clarifications for switch subjects.

43. Section 10.3.9
    Description of Change:
    Wording was added to clarify that the EOS PK assessment also applicabe for switch subjects and the wash-out requirement for switch subjects was added. The details about PK parameters were removed (specified in other sections).
    Purpose for Change: To provide clarifications for switch subjects.

44. Section 10.4
    Description of Change:
    Added more clarification about the use of Antifibrinolytics.
    Purpose for Change: To provide further clarifications.

45. Section 10.5
    Description of Change:
    Added more details about what would be recorded in the diary.
    Purpose for Change: To provide further clarifications.

46. Section 11.2, Section 12.5
    Description of Change:
    Specified the need of location for historical bleeds records. Clarified that it is good to have upto 24 months of historical records if available.
    Purpose for Change: To provide further clarifications.

47. Section 11.3
    Description of Change:
    Added more details about what would be needed for switch subjects as the historical factor dosing and consumption records.
    Purpose for Change: To provide further clarifications.

48. Section 11.5
    Description of Change:
    Clarify the assessment of overall assessment of hemostatic efficacy.
    Purpose for Change: To provide clarifications.

49. Section 11.6
    Description of Change:
    Section title was updated to add PD assessment.
    PK/PD assessment details including schedule, dosing, parameters, etc.
    Purpose for Change: To provide instruction/protocol for PK/PD assessment.

50. Section 12.1.1.1
    Description of Change:
    More details about hypersensitivity reactions were specified. SAE reporting reference was added.
    Purpose for Change: To provide further clarification.

51. Section 12.1.1.2
    Description of Change:
    More clarifications about SUSAR were added.
    Purpose for Change: To provide further clarification.

52. Section 12.1.1.3
    Description of Change:
    More details about criteria of serious AE were added.
    Purpose for Change: To provide further clarification.

53. Section 12.1.2
    Description of Change:
    Some wording of clarification was added for assessment of AE.
    Purpose for Change: To provide further clarification.

54. Section 12.1.2.2
    Description of Change:
    Original text:
    Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).
    New text:
    Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP**, is not biologically plausible per mechanism of action of the IP,** or has a much more likely alternative etiology).
    Purpose for Change: To provide more clarifications.

55. Section 12.1.2.3
    Description of Change:
    More details about hypersensitivity reactions were specified. SAE reporting reference was added.
    Purpose for Change: To provide further clarification.

56. Section 12.7
    Description of Change:
    Added clarification that height is only assessed on screening visit.
    Purpose for Change: To provide further clarification.

57. Section 12.9, Section 12.9.14.1
    Description of Change:
    "Abnormal laboratory values deemed clinically significant by the investigator are to be recorded as AEs (see Section 12.1.2)." was removed due to inaccuracy.
    New Text added: "Any abnormal laboratory value that is considered clinically significant by the investigator based on a local laboratory test result (reference range and the units to be provided) should be confirmed by a central laboratory test result **for which the sample is drawn/collected** within 24 hours of the abnormal finding by the local laboratory".
    Purpose for Change: To provide accuracy and further clarification.

58. Section 12.9.1
    Description of Change:
    Section title was updated to add PD assessment.
    Text was removed, and refered to Section 11.6.
    Purpose for Change: To avoid duplicated text.

59. Section 12.9.3.4
    Description of Change:
    Wording added to specify that only confirmed positive anti-VWF inhibitor test result will be reported and will be considered as a medically significant SAE.
    Purpose for Change: To clarify.

60. Section 12.10.2
    Description of Change:
    [redacted]
    Purpose for Change: [redacted]

61. Section 13.2.2
    Description of Change:
    Original text:
    The Full Analysis Set (FAS) will be composed of all subjects **with available bleeding data gathered during** prophylaxis IP treatment.
    New text:
    The Full Analysis Set (FAS) will be composed of all subjects **who receive** prophylaxis IP treatment.
    Purpose for Change: To re-define FAS.

62. Section 13.2.3
    Description of Change:
    Details were added on how to measure the compliance.
    Purpose for Change: To add clarifications.

63. Section 13.2.4
    Description of Change:
    Wording added to clarify PK analysis set is also for PD analysis.
    Purpose for Change: To add clarifications.

64. Section 13.4.2.2, Section 13.4.2.3
Description of Change:
[redacted]
Purpose for Change: [redacted]

65. Section 13.4.3.1, Section 13.4.3.2, Section 13.4.3.3 and Section 13.4.3.4
Description of Change:
[redacted]
Purpose for Change: [redacted]

66. Section 13.5
Description of Change:
Removed the interim analysis
Purpose for Change: No interim analysis is planned.

67. Section 15.5
Description of Change:
Additional instruction was provided to ensure the compliance by adding the text "Also, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing whenever pdVWF is used instead of rVWF. The reason for this use must also be provided to the sponsor".
Purpose for Change: To ensure compliance.

68. Section 20.1
Description of Change:
The study flow chart was updated to reflect the addition of switch cohort and to illustrate the study design for this new cohort.
Purpose for Change: To update the study design.

69. Section 20.2, Section 20.2.1
    Description of Change:
    Some clarifications were made to the tables and the footnotes, the original Table 6 was changed to 6a and specified just for on-demand subjects, Table 6b that is for switch subjects was added.
    Purpose for Change: To provide schedule for the switch subjects and to provide clarifications for surgery procedure schedule.

70. Section 20.3, Section 20.3.1
    Description of Change:
    Some clarifications were made to the tables and the footnotes, the original Table 8 was changed to 8a and specified just for on-demand subjects, Table 8b that is for switch subjects was added.
    Purpose for Change: To provide schedule for the switch subjects and to provide clarifications for surgery lab assessments.

INVESTIGATOR ACKNOWLEDGEMENT

RECOMBINANT VON WILLEBRAND FACTOR (rVWF)

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

CLINICAL TRIAL PHASE 3

LOCAL AMENDMENT 8 (CZECH REPUBLIC): 2018 MAY 18

Replaces: LOCAL AMENDMENT 5 (CZECH REPUBLIC): 2017 AUG 08

OTHER PROTOCOL ID(s)
NCT Number: NCT02973087
EudraCT Number: 2016-001478-14
IND NUMBER: 013657

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT

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Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
[redacted], MD
[redacted]
Global Clinical Development Operations
Baxalta Innovations GmbH

CLINICAL STUDY PROTOCOL

PRODUCT: Recombinant Von Willebrand Factor (rVWF, vonicog alfa)

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 SHORT TITLE: rVWF IN PROPHYLAXIS

PROTOCOL IDENTIFIER: 071301

CLINICAL TRIAL PHASE 3

LOCAL AMENDMENT 9 (TURKEY): 2018 SEP 13

Replaces:
AMENDMENT 6: 2018 MAR 12

ALL VERSIONS:
Local (Turkey) Amendment 9: 2018 SEP 13
Local (Czech Republic) Amendment 8: 2018 MAY 18
Local (Germany) Amendment 7: 2018 MAY 18
Amendment 6: 2018 MAR 12
Local (Czech) Amendment 5: 2017 AUG 08
Local (Germany) Amendment 4: 2017 AUG 04
Amendment 3: 2017 AUG 03
Amendment 2: 2016 DEC 15
Amendment 1: 2016 APR 08
Original: 2014 FEB 09

OTHER ID(s)
NCT Number: NCT02973087
EudraCT Number: 2016-001478-14
IND NUMBER: 013657

Study Sponsor(s):

Baxalta US Inc.
300 Shire Way
Lexington, MA 02421,US

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna, AUSTRIA

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted]
Global Clinical Development Operations
Baxalta Innovations GmbH

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (e.g. investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) and suspected unexpected serious adverse events (SUSARs) to the ECs.

ALL SAEs, INCLUDING SUSARs, ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT.

Bleeding events that meet seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) should be reported on the SAE eCRF and SAE Report form as an SAE.

Drug Safety contact information:

Baxalta Global Drug Safety fax number: [redacted]

OR

email: [redacted]

For definitions and information on the assessment of these events, refer to the following:

- Adverse Events (AEs), Section 12.1
- SAEs, Section 12.1.1.1
- SUSARs, Section 12.1.1.2
- Assessment of AEs, Section 12.1.2
- Safety Reporting, Section 12.1.2.3

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	Recombinant von Willebrand factor (rVWF, vonicog alpha)
Name(s) of Active Ingredient(s)	Recombinant von Willebrand factor (rVWF, vonicog alpha)
CLINICAL CONDITION(S)/INDICATION(S)	
Subjects with severe von Willebrand disease (VWD) (baseline VWF: Ristocetin cofactor activity (VWF:RCo) <20 IU/dL) requiring prophylactic treatment with coagulation factor replacement	
PROTOCOL ID	071301
PROTOCOL TITLE	A prospective, phase 3, open-label, international multicenter study on efficacy and safety of prophylaxis with rVWF in severe von Willebrand disease
Short Title	rVWF in prophylaxis
STUDY PHASE	Phase 3
PLANNED STUDY PERIOD	
Initiation	2017 OCT
Primary Completion	2019 Q4
Study Completion	2019 Q4
Duration	27 months
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
The purpose of this phase 3 study is to investigate the efficacy and safety, including immunogenicity, thrombogenicity and hypersensitivity reactions, as well as pharmacokinetics (PK), [redacted] and [redacted] of prophylactic treatment with rVWF (vonicog alfa) in adult subjects with severe VWD.	
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.	
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 FVIII activity	

Exploratory Objectives	
[redacted]	
STUDY DESIGN	
Study Type/ Classification/ Discipline	Efficacy and Safety
Control Type	No control
Study Indication Type	Prophylaxis and treatment of bleeding episodes
Intervention model	Single-group
Blinding/Masking	Open-label
Study Design	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, [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 (pdVWF switch subjects) will receive prophylactic treatment with rVWF (vonicog alfa) for a 12-month period (up to 15 months for the qualified subjects to rollover into the continuation study, if the continuation study start up is delayed beyond the completion of subject's 12-month visit).
Planned Duration of Subject Participation	Approximately 15 to 18* months * Study treatment period is extended by 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.
Primary Outcome Measure	
Efficacy • Annualized bleeding rate (ABR) for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa)	

Secondary Outcome Measures

Additional efficacy of prophylactic treatment with rVWF (vonicog alfa)

- ABR percent reduction success for OD subjects defined as at least 25% reduction of ABR for spontaneous (not related to trauma) bleeding episodes during rVWF (vonicog alfa) prophylaxis relative to the subject's own historical ABR during on-demand treatment
- ABR preservation success for pdVWF switch subjects 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 during prophylactic treatment with pdVWF
- Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 bleeding episodes during the 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
- Spontaneous ABR 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)

Safety

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

Pharmacokinetics (PK) and Pharmacodynamics (PD)

- PK parameters after a washout for on-demand 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 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 VWF:RCo, Von Willebrand factor antigen (VWF:Ag), Von Willebrand collagen binding activity (VWF:CB).
- PD parameters after a washout for on-demand subjects: C_{max}, T_{max}, and $AUC_{0-tlast}$ as measured in FVIII activity by the 1-stage clotting assay (FVIII:C).
- PK parameters at steady state for on-demand and switch subjects: area under the concentration versus time curve from 0 to end of the partial dosing interval ($AUC_{0-tau;ss}$), 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. PK parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.

- PD parameters at steady state for on-demand and switch subjects: $AUC_{0\text{-}tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$ as measured in FVIII actvitiy by the 1-stage clotting assay (FVIII:C). PD parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.
- Time course of FVIII clotting activity (FVIII:C) levels.

Exploratory Outcome Measures

[redacted]

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**Dosage form**: powder and solvent for solution for injection **Dosage frequency**: <u>Prophylactic Treatment</u> Subjects transitioning from on-demand treatment will receive twice weekly infusion with rVWF (vonicog alfa) at doses of 50 ± 10 IU/kg rVWF:RCo. Dosage may be individualized within this range based on: • available historical PK data • type and severity of bleeding episodes the subject has experienced in the past • monitoring of appropriate clinical and laboratory measures The starting dose can, after consultation with the Sponsor, be increased up to 80 U/kg if considered necessary to assure effective prophylaxis. Subjects switching from pdVWF prophylaxis treatment: the weekly dose (IU/kg) of rVWF (vonicog alfa) for each patient will be equivalent (± 10%) to the weekly VWF dose received during prophylactic treatment with pdVWF. The weekly dose should be divided into 2 infusions, 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. A once weekly dose regimen will be allowed after switch to rVWF (vonicog alfa) if the patient has been on a once weekly dose regimen with pdVWF. Dose and dose interval may, after consultation with the sponsor, be further individualized based on: • available historical PK data • type and severity of bleeding episodes the subject has experienced in the past • monitoring of appropriate clinical and laboratory measures <u>Treatment of Bleeding Episodes:</u> Dosage must be individualized based on the subject's weight, type and severity of bleeding episode and monitoring of appropriate clinical and laboratory measures. In general, an initial dose of 40-60 IU/kg VWF:RCo with or without 30-45 IU rFVIII [ADVATE, octocog alfa]/kg is recommended (rVWF:rFVIII ratio of 1.3:1: ± 0.2). In cases of major bleeding episodes, a dose of up to 80 IU/kg VWF:RCo may be infused. Subsequent doses, if necessary, will be administered with or without ADVATE (rFVIII, octocog alfa) to maintain VWF:RCo and FVIII levels for as long as deemed necessary by the investigator. **Mode of Administration:** intravenous

SUBJECT SELECTION	
Targeted Accrual	Approximately 22 adult subjects with severe VWD will be included to have ≥8 subjects in each cohort (OD and switch). A total of at least 5 type 3 VWD subjects will be followed for 12 months.
Number of Groups/ Arms/ Cohorts	Single-group

Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding:
    a. Type 1 (VWF:RCo <20 IU/dL) or,
    b. Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2M or,
    c. Type 3 (VWF:Ag ≤3 IU/dL).
2. Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.
3. For on-demand patient group, subject currently receiving on-demand treatment for whom prophylactic treatment is recommended by the investigator.
4. For pdVWF switch patient group, subject has been receiving prophylactic treatment of pdVWF products for no less than 12 months prior to screening.
5. For on-demand patient group, subject has ≥3 documented spontaneous bleeds (not including menorrhagia) requiring VWF treatment during the past 12 months.
6. Availability of records to reliably evaluate type, frequency and treatment of bleeding episodes during at least 12 months preceding enrollment. Up to 24 months of retrospective data should be collected if available. Availability of dosing and factor consumption during 12 months (up to 24 months) of treatment prior to enrollment is required for pdVWF switch subjects and is desired (but not a requirement) for on-demand subjects.
7. Subject is ≥18 years old at the time of screening and has a body mass index ≥15 but <40 kg/m^2.
8. If female of childbearing potential, subject presents with a negative blood/urine pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.
9. Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

Subjects who meet ANY of the following criteria are not eligible for this study:

1. The subject has been diagnosed with Type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD (e.g., qualitative and quantitative platelet disorders or elevated prothrombin time (PT)/international normalized ratio [INR] >1.4).
2. The subject is currently receiving prophylactic treatment with more than 5 infusions per week.
3. The subject is currently receiving prophylactic treatment with a weekly dose exceeding 240 IU/kg.
4. The subject has a history or presence of a VWF inhibitor at screening.
5. The subject has a history or presence of a FVIII inhibitor with a titer ≥0.4 Bethesda units (BU) (by Nijmegen modified Bethesda assay) or ≥0.6 BU (by Bethesda assay).

6. The subject has a known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins.
7. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
8. The subject has a medical history of a thromboembolic event.
9. The subject is human immunodeficiency virus (HIV) positive with an absolute Helper T cell (CD4) count <200/mm^3.
10. The subject has been diagnosed with significant liver disease per investigator's medical assessment of the subject's current condition or medical history or as evidenced by any of the following: serum alanine aminotransferase (ALT) greater than 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).
11. The subject has been diagnosed with renal disease, with a serum creatinine (CR) level ≥2.5 mg/dL.
12. The subject has a platelet count <100,000/mL at screening.
13. The subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to signing the informed consent.
14. The subject is pregnant or lactating at the time of enrollment.
15. Patient has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
16. The subject has participated in another clinical study involving another investigational product (IP) or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
17. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
18. The subject is scheduled for a surgical intervention.
19. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
20. The subject has a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
21. The subject is in prison or compulsory detention by regulatory and/or juridical order
22. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.

Delay criteria

1. If the subject presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) the screening visit will be postponed until the subject has recovered.

STATISTICAL ANALYSIS

Sample Size Calculation

Approximately 22 adult subjects with severe VWD will be included in the study. The aim is to have ≥8 subjects in each cohort (OD and switch). A total of at least five type 3 VWD subjects will be followed for 12 months. 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).[1]

Planned Statistical Analysis

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

The Safety Analysis Set will be composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

The Per-Protocol (PP) Analysis Set will be composed of subjects who are at least 70% compliant regarding the number of scheduled prophylactic infusions. Only subjects who meet all study entry criteria and who have no major protocol violations that might impact primary efficacy assessments will be included in the PP analysis set.

The Pharmacokinetic Full Analysis Set (PKFAS) will be composed of all subjects who received the PK infusion and who provided acceptable data for PK and PD analysis. Acceptable PK/PD data will be defined in the Statistical Analysis Plan.

Primary Outcome Measure:

No formal statistical hypothesis test is planned for the analysis. Spontaneous ABR while treated with rVWF (vonicog alfa) for each cohort, on demand and switch subjects, will be estimated using a negative binomial regression. The prior ABR for each cohort will be based on historical data collected from each enrolled subject. The two ABRs (observed on the study and historical) will be assessed 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 ABR ratio together with a two-sided, 95% confidence interval (CI) will be reported for each cohort.

The difference in on-study ABR relative to historical ABR will be summarized descriptively.

The primary efficacy analysis will be based on the FAS and will be summarized by the two cohorts: on-demand and switch subjects. As a supportive analysis, the same analysis will also be carried out on the per-PP analysis set.

Secondary Outcome Measures:

In general, data for secondary efficacy analysis will be summarized by the two cohorts: on-demand and switch subjects and when applicable overall. Mean, standard deviation, median, range, quartiles will be calculated for continuous endpoints. Proportions will be calculated for categorical endpoints. Confidence intervals at the 95% level will be provided when appropriate.

Additional efficacy of prophylactic treatment with rVWF (vonicog alfa):

The number and proportion of on-demand subjects with ABR percent reduction success (i.e. ≥ 25%) will be calculated together with a two-sided 95% CI for the proportion.

The number and proportion of pdVWF switch subjects with ABR preservation success will be reported together with the corresponding 95% two-sided CIs for the proportion.

The number and proportion of subjects with categorized spontaneous ABR (i.e. 0, 1-2, 3-5, more than 5 bleeds) will be reported descriptively.

Summary statistics for the total number of infusions, as well as average number of infusions per week will be provided. The total weight adjusted consumption of rVWF (vonicog alfa) during prophylactic treatment will be provided. If applicable, historical data on consumption of pdVWF prior to the study will be summarized as well.

The change in spontaneous ABR from the historical rate to that during the rVWF (vonicog alfa) prophylaxis period will be summarized by location of bleeding (GI, epistaxis, joint bleeding, menorrhagia, oral and other mucosa, muscle and soft tissue, etc.).

Pharmacokinetics (PK) and Pharmacodynamics (PD):

The following PK parameters, based on the initial PK assessment after a washout for on-demand subjects, will be listed and summarized descriptively for VWF:RCo, VWF:Ag and VWF:CB: IR, $T_{1/2}$, MRT, $AUC_{0-\infty}$, $AUC_{0\text{-tlast}}$, C_{max}, T_{max}, V_{ss}, and CL. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity (FVIII:C), based on the initial PK assessment after a washout for on-demand subjects will be assessed using C_{max}, T_{max}, and $AUC_{0\text{-tlast}}$. These PD parameters will be listed and summarized descriptively.

PK parameters at steady state ($AUC_{0\text{-tau;ss}}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$) for the partial dosing interval will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study for VWF:RCo, VWF:Ag and VWF:CB and summarized descriptively for subjects with the same dosing regimens. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity (FVIII:C) will be assessed using $AUC_{0\text{-tau;ss}}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$. These PD parameters will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study and will be summarized descriptively for subjects with the same dosing regimens.

For the on-demand subjects, the PK of VWF:RCo will be analyzed using a population PK approach to characterize the single and multiple dose pharmacokinetics, including associated variability, of VWF:RCo in the study population.

For the switch subjects, differences in $AUC_{0\text{-tau;ss}}$, $C_{max;ss}$, and $C_{min;ss}$ assessess shortly after reaching steady state and assessed at the end of the study will be assessed by ratio of geometric means and corresponding two-sided 95% confidence intervals for VWF:RCo, VWF:Ag, VWF:CB, and FVIII:C. 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.

Descriptive statistics will be used to summarize VWF:RCo, VWF:Ag, VWF:CB, and FVIII:C levels for each nominal time point on the PK curve. For all subjects activity/concentration vs. time curves will be prepared.

Safety:

Safety analysis will be performed overall and by the two cohorts: on-demand and switch subjects.

Treatment-emergent AEs (TEAEs) are defined as AEs with start dates on or after the first exposure to IP. Summaries of AEs will be based on TEAEs unless otherwise indicated.

Occurrence of AEs and serious AEs (SAEs) will be summarized descriptively, by system organ class and preferred term. The number and percentage of subjects who experienced AEs and SAEs, and the number of AEs and SAEs will be tabulated. In addition, the number of subjects who experienced AEs assessed as related to IP by the investigator, and the number of IP-related AEs will be tabulated. The number of patients with AEs by severity will be presented similarly.

A listing of all AEs will be presented by subject identifier, age, sex, preferred term and 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.

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 infusion, irrespective of being related or not related to treatment. Temporally associated AEs will be presented in summary tables.

Adverse events of special interest (AESI), such as hypersensitivity reactions and thromboembolic events, will be monitored throughout the study and statistical analysis will be conducted based on the search criteria (eg, standardized MedDRA queries [SMQ]) determined prior to database lock, and summarized.

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.

Clinically significant changes relative to baseline in vital signs and clinical laboratory parameters (hematology, clinical chemistry) will be reported.

4. TABLE OF CONTENTS

Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABR	Annualized bleeding rate
ADAMTS13	A Disintegrin And Metalloproteinase with a Thrombospondin type 1 motif, number 13
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the plasma concentration /time curve from time 0 to infinity
$AUC_{0-tau;ss}$	Area under the plasma concentration /time curve from time 0 to end of the partial dosing interval
$AUC_{0-tlast}$	Area under the plasma concentration /time curve from 0 to the last measurable concentration
aPTT	Activated partial thromboplastin time
B19V	Parvovirus B19
BP	Blood pressure
BU	Bethesda Unit
BUN	Blood urea nitrogen
BW	Body weight
CAM	Cell adhesion molecule
CBC	Complete blood count
CD4	Helper T cell
CHO	Chinese hamster ovary
CI	Confidence interval
Cl	Chloride
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max;ss}$	Maximum plasma concentration during the partial dosing interval at steady state
$C_{min;ss}$	Minimum plasma concentration during the partial dosing interval at steady state
CR	Creatinine
CTA	Clinical Trial Agreement
eCRF	Electronic case report form
DMC	Data monitoring committee
DIC	Disseminated intravascular coagulation

Abbreviation	Definition
DVT	Deep vein thrombosis
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
[redacted]	[redacted]
FAS	Full analysis set
FVIII	Factor VIII
FVIII:C	Factor VIII clotting activity
GCP	Good Clinical Practice
GI	Gastrointestinal
Glu	Glucose
HAMA	Human anti- mouse antibodies
HAV	Hepatitis A virus
HB	Hepatitis B
HBs	Hepatitis B surface
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
[redacted]	[redacted]
HRP	Horseradish peroxidase
IB	Investigator's brochure
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
INR	International normalized ratio
IP	Investigational product
IR	Incremental recovery
i.v.	Intravenous

Abbreviation	Definition
K	Potassium
k.o.	Knock out
LDH	Lactate Dehydrogenase
Na	Sodium
NMC	Non-medical complaint
NOAEL	No observed adverse effect level
MRI	Magnetic resonance imaging
MRT	Mean residence time
pdVWF	Plasma derived VWF product
pdVWF/FVIII	Plasma derived VWF product containing fractions of FVIII
PBAC	Pictorial Blood Assessment Chart
PCR	Polymerase Chain Reaction
PEF	Peak expiratory flow
PK	Pharmacokinetic
PKFAS	Pharmacokinetic Full Analysis Set
PKPPAS	Pharmacokinetic Per Protocol Analysis Set
PP	Per protocol
PT	Prothrombin time
Q1, Q3	Quartile
rFVIII	Recombinant factor VIII
rVWF	Recombinant von Willebrand factor
RBC	Red blood cell count
SAE	Serious adverse event
SAER	Serious adverse event report
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
[redacted]	[redacted]
SIC	Subject identification code
SMQ	Standardised MedDRA queries
sP-selectin	Soluble P-selectin
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Terminal phase half life
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack

Abbreviation	Definition
T_{max}	Minimum time to reach the maximum concentration
$T_{max;ss}$	Minimum time to reach the maximum concentration at steady state
TTP	Thrombotic thrombocytopenic purpura
ULMW	Ultra-large molecular weight
ULN	Upper limit of normal
V_{ss}	Volume of distribution at steady state
[redacted]	[redacted]
VTE	Venous thromboembolism
VWD	von Willebrand disease
VWF	Von Willebrand factor
VWF:Ag	Von Willebrand factor antigen
VWF:CB	Von Willebrand Factor collagen binding
VWF:RCo	Von Willebrand factor: Ristocetin cofactor activity
WBC	White blood cell

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

Baxalta US Inc. (hereafter referred to as Baxalta or sponsor) has developed a human recombinant von Willebrand Factor (rVWF, vonicog alpha), which is co-expressed with recombinant factor VIII (rFVIII) in a Chinese hamster ovary (CHO) cell line and separated during the subsequent downstream process. To address concerns regarding the risk of transmission of blood-borne pathogens that may be introduced by human plasma, no exogenously added raw materials of human or animal origin are employed in the cell culture, purification, or formulation of the final container product. The only proteins present in the final container product other than rVWF (vonicog alfa) are trace quantities of murine immunoglobulin (IgG, from the immunoaffinity purification), host cell (i.e., CHO) protein, rFurin (used to further process rVWF). rVWF (vonicog alfa) is intended for the treatment of von Willebrand disease (VWD).

rVWF (vonicog alfa) has been developed under the Baxalta internal code BAX111 and is used as investigational product (IP) in this study. rVWF (vonicog alfa) may be used with or without ADVATE (rFVIII, octocog alfa) for the treatment of bleeding episodes (see Section 8.6.4.4). See Section 8.6 for further information on the IPs and their usage in this study. A detailed description of rVWF (vonicog alfa) is also provided in the Investigator's Brochure (IB).

rVWF (vonicog alfa) was granted licensure in the United States in December 2015 under the brand name VONVENDI for the on-demand treatment and control of bleeding episodes in adults diagnosed with VWD and it has been available on the market in the US since 09 August 2016. In April 2018, VONVENDI was also granted licensure in the US by the FDA for an additional indication of perioperative management of bleeding in adults (age 18 and older) diagnosed with VWD. On 31st of August 2018, European Commission implemented the decision for granting marketing authorization for VEYVONDI (vonicog alfa) for the treatment of haemorrhage and surgical bleeding and for the prevention of surgical bleeding in adults (age 18 and older) diagnosed with VWD, when desmopressin (DDAVP) treatment alone is ineffective or not indicated.

6.2 Clinical Condition/Indication

Von Willebrand Factor (VWF) is a large multimeric glycoprotein with a molecular weight that varies from 500 to 20,000 kDa. VWF is normally found in plasma and produced in the alpha-granules of platelets and in endothelial cell organelles known as the Weibel-Palade bodies. VWF mediates platelet adhesion and aggregation at sites of vascular injury, one of the key functions in primary hemostasis. VWF also serves to stabilize coagulation factor VIII (FVIII), where FVIII is an essential cofactor of secondary hemostasis, which leads to fibrin clot formation.[2] Qualitative and/or quantitative deficiencies of VWF lead to a highly variable bleeding diathesis known as VWD, the most common of the hereditary coagulation factor deficiencies. Penetrance of VWD is highly variable, with only a small fraction of mildly affected patients displaying clinical symptoms or a family history of a bleeding diathesis.

The current biochemical-based classification distinguishes disorders arising from partial quantitative (type 1), qualitative (type 2), or virtually complete (type 3) deficiencies of VWF. Up to 70% of VWD patients are diagnosed with type 1 VWD, which may also be associated with minor functional defects in the molecule. In general, patients with type 1 VWD display mild clinical symptoms. Approximately 20 to 30% of VWD patients are diagnosed with type 2 VWD. Type 2 VWD is further divided into 4 subtypes (A, B, N, and M), reflecting distinct classes of functional abnormalities. These defects result in abnormal functional and/or multimeric distribution patterns that facilitate their diagnosis. The bleeding diathesis is usually moderate and primarily affects the mucosal tissues. Type 2N VWD patients are sometimes misdiagnosed as mild hemophilia A. Finally, approximately 1% percent of VWD patients exhibit a total or near total absence of VWF, which is classified as type 3 VWD. The incidence of type 3 VWD is estimated at $0.5\text{-}1.0 \times 10^{6}$. This type is also associated with a very low FVIII level (typically <5%) because the VWF carrier function for FVIII is lost. Replacement of VWF alone stabilizes endogenous FVIII, resulting in hemostatic levels within several hours post-infusion. Published results from studies of a plasma-derived VWF (pdVWF) concentrate demonstrated an increase of FVIII at an approximate rate of 5.8 ± 1 IU dL^{-1} h^{-1}.[3] Type 3 VWD patients display severe hemorrhagic symptoms with bleeding predominantly in mucosal tissues, muscle and joints. All VWD patients, particularly those with type 2 or type 3 VWD, are at an increased risk for life-threatening bleeding episodes.

6.3 The Role of Prophylaxis in the Management of VWD

The goals of long term prophylaxis in VWD are to maintain VWF and FVIII at sufficient levels to reduce the frequency and duration of bleeding episodes, the need for red blood cell transfusions, and the risk of complications, such as arthropathy.[4] In contrast to hemophilia, routine prophylaxis is not as established in VWD, although prophylaxis for patients with severe VWD was in use in Sweden already during the 1950s.[5] In those early days of VWD treatment, plasma FVIII concentrates containing VWF fractions were applied for replacement therapy, which then were followed by plasma derived VWF products containing fractions of FVIII (pdVWF/FVIII).

A Swedish cohort including 37 patients with type 3 VWD under prophylactic median treatment of 11 years (range 2 to 45 years) was retrospectively analyzed.[6,7] The doses used for prophylaxis, given once weekly for at least 45 weeks per year, were calculated based on 12 to 50 IU/kg body weight (BW) of FVIII clotting activity (FVIII:C) which approximately corresponded to 24-100 IU/kg von Willebrand factor: Ristocetin cofactor activity (VWF:RCo) considering that mainly Haemate with a known VWF:RCo/FVIII:C ratio of about 2 was used. An escalation of doses from 1 to 3 dose levels was allowed depending on the frequency and severity of bleeding episodes. The results demonstrate that under long-term prophylaxis the number of bleeds could be reduced dramatically. Whereas the median value for bleeds per year was about 10 before prophylaxis this value could be reduced to less than 1 bleed per year during prophylaxis.

The benefit of prophylaxis for such indications was retrospectively also demonstrated in a cohort of Italian patients including type 3, 2A, 2M and type 1 patients. Prophylaxis was started after severe gastrointestinal or joint bleeding episodes and completely prevented bleeding episodes in 8 of these 11 patients and largely reduced the need of blood transfusions in the remaining 3. A regimen of 40 IU rVWF:RCo/kg was applied every other day or twice a week. A prospective study on prophylaxis, the PRO.WILL study, has been initiated in Italy.[8]

The results of a prospective study investigating the prophylaxis in children and young adults showed a significantly reduced bleeding frequency and bleeding score (3 vs. 0.07; 3 vs. 0. $p<0.001$) compared to the pre-prophylaxis values. The median dose was 40 (20-47) IU/kg VWF:RCo administered mainly twice weekly in 23 patients, 3 times a week in 7 patients and 4 times a week in 2 children.[9]

The VWD Prophylaxis Network initiated the VWD International Prophylaxis (VIP) trial to investigate the role of prophylaxis in patients with severe VWD including Type 1, 2, and 3. The dose of the factor replacement product was 50 IU /kgVWF:RCo.

The frequency of the dose depended on the type of bleeding and could be increased from once weekly to twice weekly or 3 times per week. For the treatment of menorrhagia the dose of 50 IU/kg VWF:RCo was given on the first day of menses for 2 cycles. The frequency could be increased to Day 1 and 2 for 2 cycles or to Day 1, 2, and 3 of menses.

The study contains both retrospective and prospective study components. Results from the retrospective study component were published, including 61 subjects on prophylactic regimen in the past 6 months prior to enrollment or subjects with a history of prophylaxis over at least 6 month.[10] Differences in annualized bleeding rates (ABR) within individuals (during prophylaxis – before prophylaxis) were significant for those with primary indications of epistaxis (P = 0.0005), joint bleeding (P = 0.002) and GI bleeding (P = 0.001). The difference in the group whose primary indication for treatment was abnormally heavy bleeding at menstruation (n = 4) was not significant (P = 0.25). The reduction of mucosal bleeding likely not only dependents on normal circulating levels of active VWF, but also on the presence of discrete concentrations of normal VWF inside the platelets and within endothelial matrices. The low subject number (n=4) and the treatment scheme for menorrhagia on Days 1, 2, and 3 of menses which might represent rather on-demand than prophylactic treatment may also account for the outcome in this study.

Results from the prospective study component were reported recently.[11] Eleven subjects completed the study. Six subjects had type 2A, and 5 subjects had type 3 VWD. Six subjects presented with epistaxis, 3 with GI bleeding, and 2 with joint bleeding. Seven subjects had dose escalation above the first level. Among the 10 subjects with evaluable bleeding log data, the use of prophylaxis decreased the median ABR from 25 to 6.1 (95% confidence interval [CI] of the rate difference: -51.6 to -1.7), and the median ABR was even lower (4.0; 95% CI: -57.5 to -5.3) when the subjects reached their final dosing level. The authors concluded that this was the first prospective study to demonstrate that prophylaxis with VWF concentrates is highly effective in reducing mucosal and joint bleeding rates in clinically severe VWD.

The results of the VIP study and previous investigations suggest that VWD patients with recurrent bleeding episodes and severe menorrhagia will benefit from a prophylactic VWF replacement therapy. There is evidence that up to 40% of patients with type 3 VWD experience joint bleeding which can lead to hemophilic arthropathy. Other potential indications for prophylaxis include patients with type 2A or 2B VWD with recurrent gastrointestinal bleeding, menorrhagia or frequent epistaxis.[4] Long-term prophylaxis for most patients with type 3 VWD and in some patients with type 1 or 2 VWD, depending on the pattern of bleeding, may be the treatment option of choice.

Although the main experience with long-term prophylaxis is with secondary prophylaxis, primary prophylaxis starting at young age is recommended to prevent arthropathy in patients with severe VWD.[12]

However, further studies are needed to develop evidence-based guidelines for prophylactic treatment in VWD.

6.4 Populations to be Studied

A total of approximately 22 eligible, adult subjects with severe VWD (baseline VWF:RCo <20 IU/dL) are planned to be enrolled. Two cohorts of patients will be included: patients currently receiving on-demand VWF treatment (OD subjects) and patients currently on prophylactic treatment with pdVWF (pdVWF switch subjects), and the aim is to have ≥8 subjects in each of the 2 cohorts, with a total of at least 5 type 3 VWD subjects followed for 12 months. Enrolled subjects (i.e., subjects who have signed the informed consent form) will be eligible to participate in the study if they meet all of the inclusion criteria (see Section 9.1) and none of the exclusion criteria (see Section 9.2).

6.5 Findings from Nonclinical and Clinical Studies

The following summarizes the key findings from relevant nonclinical studies as well as from the completed clinical studies **070701** (Phase 1 pharmacokinetics [PK] and safety in VWD), **071001** (Phase 3 safety and efficacy in the treatment of bleeding episodes in VWD), **071101** (Phase 3 efficacy and safety in VWD subjects undergo elective surgical procedures), **071104** (Phase 1 safety and PK in hemophilia A), and **071401** (Phase 3, expanded access in a single subject with VWD). Potential risks and efficacy of rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) are summarized in the following sections. For additional information on nonclinical and clinical Phase 1 results refer to the rVWF (vonicog alfa) IB.

6.5.1 Findings from Nonclinical Studies

6.5.1.1 Primary Pharmacodynamics

Efficacy of rVWF (vonicog alfa) combined with ADVATE (rFVIII, octocog alfa) was shown in VWD animal models, which have also low endogenous FVIII levels. Time to occlusion and stable thrombus formation was assessed in the carotid occlusion model in VWD mice. The results demonstrated that rVWF (vonicog alfa) in combination with ADVATE (rFVIII, octocog alfa) acted efficiently in a dose-dependent manner and had higher efficacy than rVWF (vonicog alfa) alone or plasma derived (pd)VWF. These results were confirmed in an additional study assessing blood loss and survival in a tail tip bleeding model in VWD mice. In a VWD dog, rVWF (vonicog alfa) stabilized canine FVIII in the circulation and significantly reduced the bleeding time.

6.5.1.2 Safety Pharmacology

The anaphylactoid and thrombogenic potential of the co-infusion of ADVATE (rFVIII, octocog alfa) and rVWF (vonicog alfa) and the co-infused product's effects on blood pressure, cardiac and respiratory function and parameters of coagulation activation were investigated in 4 in vivo studies in different animal models. Safety pharmacology studies in rats, guinea pigs, rabbits, and dogs revealed no risks for anaphylactoid and thrombogenic potential of ADVATE (rFVIII, octocog alfa) in combination with rVWF (vonicog alfa). All observations in safety pharmacology studies are considered to lie within the biological variability of animal models or occurred due to known species-specific anaphylactoid effects of excipients.

6.5.1.3 Pharmacokinetics

Pharmacokinetic studies of both rVWF (vonicog alfa) alone and combined with human rFVIII (rVWF+ADVATE) were conducted in VWD mice, VWD dogs, VWD pigs, rats, and cynomolgus monkeys. Human rVWF (vonicog alfa) stabilized the endogenous FVIII in VWD mice, VWD pigs, and VWD dogs. Furthermore, the hypotheses that the area under the curve (AUC) with rVWF alone and rVWF+ADVATE is not inferior to the AUC with pdVWF (Haemate P) was tested and confirmed statistically in normal rats. The PK characteristics of ADVATE (rFVIII, octocog alfa) were not affected by co-administration of rVWF (vonicog alfa) in cynomolgus monkeys. The PK data in the FVIII knock out (k.o.) mice model are inconclusive and might not be relevant for the clinical situation. However, a stabilizing effect of VWF on FVIII could be shown in a double k.o. model in a dose dependent manner.

6.5.1.4 Toxicology

Single dose toxicity studies were conducted in C57BL/6J-mice, VWD mice, rats, rabbits, and cynomolgus monkeys. Rats, rabbits, and cynomolgus monkeys showed no signs of toxicity. Signs of microthrombosis, an exaggerated pharmacological effect, were observed in mice. Mice are not capable of sufficiently cleaving the rVWF (vonicog alfa) subunit as murine disintegrin and metalloproteinase with a thrombospondin type 1 motif, number 13 (ADAMTS13) does not decrease the ultra-large molecular weight multimers of rVWF (vonicog alfa).[13] The observed symptoms of microthrombosis are interpreted as a species-specific exaggerated pharmacological effect. Studies evaluating the safety of repeated administration of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) (daily over 14 days) were performed in a rodent (rat) and non-rodent (cynomolgus monkey) species. Reversible signs of exaggerated pharmacological effects (regenerative anemia, thrombocytopenia, and treatment-related histopathologic changes in the heart, liver, and spleen) were observed in rats that were administered 1400 U VWF:RCo/kg /day + 1080 IU ADVATE/kg/day intravenously once daily for 14 days.

Also, these findings are interpreted as a species-specific exaggerated pharmacological effect due to the low susceptibility of human rVWF (vonicog alfa) to cleavage by rodent ADAMTS13.[13] No toxicologically relevant changes were evident for clinical observations, body weight, feed consumption, ophthalmology, urinalysis, coagulation, and serum chemistry parameters, platelet aggregation, and gross pathology. rVWF (vonicog alfa) combined with ADVATE (rFVIII, octocog alfa) was well tolerated in cynomolgus monkeys after daily intravenous (i.v.) (bolus) administration of 100 U VWF:RCo/kg rVWF (vonicog alfa) combined with 77 IU/kg ADVATE (rFVIII, octocog alfa) over a period of 14 days. No adverse effects could be detected in this species. There were no signs of hemolysis, thrombosis, or thrombocytopenia after repeated intravenous application of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa). Therefore, 100 U VWF:RCo/kg/day rVWF (vonicog alfa) with or without 77 IU/kg ADVATE (rFVIII, octocog alfa) was considered the no observed adverse effect level (NOAEL) in this study, which was the highest dose tested. Anti-drug antibodies, however, were formed in both species and resulted in a significant reduction in drug exposure after 14 applications as compared to a single application. These antibodies substantially reduced the systemic exposure to the test substance as compared to a single dose administration. No adverse effects due to antibody formation were observed in both species.

rVWF (vonicog alfa) combined with ADVATE (rFVIII, octocog alfa) was well tolerated locally and no genotoxic potential was evident after 2 in vitro and 1 in vivo genotoxicity study. A study on the influence of co-administration of VWF and ADVATE (rFVIII, octocog alfa) on the immunogenicity of ADVATE (rFVIII, octocog alfa) in 3 different hemophilic mouse models (E17 hemophilic Balb/c mice, E17 hemophilic C57BL/6J mice, and E17 hemophilic human F8 transgenic mice) showed that rVWF (vonicog alfa) does not negatively impact the immunogenicity of ADVATE (rFVIII, octocog alfa) in any of the three different hemophilic mouse models.

6.5.2 Findings from Clinical Studies

The clinical safety, efficacy and PK were assessed in 4 completed trials: one phase 1 study (**070701)**) and two phase 3 studies (**071001** and **071101**) that enrolled patients with VWD; one phase 1 study (**071104**) that enrolled patients with hemophilia A. Details on study design, populations enrolled, and safety and efficacy outcomes of the phase 1 studies are presented in Section 6.5.2.1 and Section 6.5.2.2, the phase 3 study in Section 6.5.2.3, and the phase 3 surgery study in Section 6.5.2.4. Information on a single subject with VWD in Study **071401** is presented in Section 6.5.2.5.

6.5.2.1 Study 070701

Phase 1 clinical study **070701** was a multicenter, controlled, randomized, single-blind, prospective 3-step, dose escalation study to investigate safety, tolerability, and PK of rVWF (vonicog alfa) combined at a fixed ratio with ADVATE (VWF:RCo/FVIII:C of 1.3 ± 0.2:1) in adults with severe VWD.[14] Subjects were enrolled in sequential cohorts in a dose escalating manner: Cohort 1, 2, and 3 received a single intravenous infusion of rVWF:ADVATE at the following doses: 2 IU/kg VWF:RCo (Cohort 1), 7.5 IU/kg VWF:RCo (Cohort 2), and 20 IU/kg VWF:RCo (Cohort 3). Subjects in Cohort 4 received a single intravenous infusion of rVWF:ADVATE and pdVWF/ADVATE at 50 IU/kg VWF:RCo in random order.

The primary endpoint was the tolerability and safety after single dose injections of rVWF:ADVATE at 2, 7.5, 20, and 50 IU/kg VWF:RCo for up to 30 days after the last IP infusion. The data generated in this phase 1 study suggest that rVWF:ADVATE up to the highest investigated dose of 50 IU/kg VWF:RCo is well tolerated and safe in adults with severe VWD. No thrombogenic risk or thrombotic thrombocytopenic purpura (TTP)-like syndrome was observed, and no neutralizing antibodies to VWF or FVIII were identified. There were no deaths or other serious adverse reactions, and no infusions were interrupted or stopped due to an AE. Overall, the reported AE profile was similar between the recombinant and plasma-derived concentrates.

Secondary endpoints were the PK assessment of VWF:RCo, von Willebrand factor antigen (VWF:Ag) and multimeric composition of rVWF (vonicog alfa) as well as FVIII:C at standardized time points after single injections of rVWF:ADVATE and pdVWF:FVIII.

The median VWF:RCo terminal half-life ($T_{1/2}$) of rVWF (vonicog alfa) at the 50 IU/kg dose was 16 hours. $T_{1/2}$ with pdVWF:FVIII at the same dose level appeared shorter at 12.58 hours, however, the limits of the 90% CI were similar (11.73 to 17.7 hours vs. 11.87 to 18.03 hours). The median $T_{1/2}$ of VWF:RCo were shorter with the lower investigated doses: 7.13 hours and 13.23 hours with the 7.5 IU/kg and 20 IU/kg doses, although these data were derived from a much smaller number of subjects.

In consequence of the missing ADAMTS13 cleavage, ultra-large molecular weight (ULMW) multimers are contained in the rVWF (vonicog alfa) final product. The immediate cleavage of these ultra-large multimers by ADAMTS13 upon release into the circulation could be demonstrated applying sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE)/Immunoblot with polyclonal anti-VWF antibodies to detect the resulting rVWF (vonicog alfa) subunit cleavage fragments.

Overall the data generated in this phase 1 study suggest that rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) is well tolerated and safe in adults with severe VWD.

6.5.2.2 Study 071104

This study was a prospective, uncontrolled, non-randomized, multicenter proof of concept study to assess safety and PK of the addition of rVWF (vonicog alfa) to ADVATE (rFVIII, octocog alfa) treatment in 12 evaluable subjects with severe hemophilia A. All subjects underwent 3 PK analyses: the first after infusion with ADVATE (rFVIII, octocog alfa) alone, the second after infusion with ADVATE (rFVIII, octocog alfa) plus 10 IU/kg rVWF (vonicog alfa) and the third after infusion with ADVATE (rFVIII, octocog alfa) plus 50 IU/kg rVWF (vonicog alfa).

The PK analysis was performed at intervals of approximately 8 to 14 days. Before each infusion for PK assessment, there was a wash-out period of at least 5 days and the subjects were not actively bleeding.

Primary outcome measures indicate that co-administration of rVWF (vonicog alfa) slightly sustain ADVATE activity with the highest observed ADVATE (rFVIII, octocog alfa) half-life of 13.74 h (CI 11.44 to 16.52) after co-infusion of 50 IU/kg ADVATE plus 50 IU/kg rVWF:RCo.

The highest improvement in ADVATE (rFVIII, octocog alfa) circulating half-life was observed in subjects with VWF:Ag levels below 100% which indicates an association between baseline VWF:Ag levels and ADVATE (rFVIII, octocog alfa) half-life increase.

No treatment related AEs or SAEs were reported. No subject withdrew due to an AE and there were no deaths. No binding antibodies to VWF, CHO, and rFurin were detectable in the confirmatory assay and no signs of a hypersensitivity to rVWF (vonicog alfa) or ADVATE (rFVIII, octocog alfa) antigen were observed. Laboratory values over time did not indicate any potential safety risk for hemophilia A patients treated with rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) in combination.

In summary, the data indicate that rVWF (vonicog alfa) co-administered with ADVATE (rFVIII, octocog alfa) up to the highest dose of 50 IU/kg VWF:RCo is well tolerated and safe in hemophilia A patients.

6.5.2.3 Study 071001

This was a phase 3, multicenter, open-label, part-randomized clinical study to assess the PK, safety, and efficacy of rVWF:rFVIII and rVWF in the treatment of bleeding episodes in adult subjects with severe type 3 and severe non-type 3 VWD.[15] A total of 49 subjects were enrolled (signed informed consent) and screened, 18 subjects were randomized (randomization only applies to Arm 1[PK50 with treatment of BE] and Arm 2 [PK50 only] see below), 37 subjects were treated with IP (all study arms), and 30 subjects completed the study.

The study consisted of 2 parts (Part A and Part B). Part A consisted of PK assessments alone (Arm 2: PK50 only [without treatment of bleeding episodes]), or PK assessments (Arm 1: PK50 and Arm 3: PK80) plus on-demand treatment period(s) of 6 months for bleeding episodes, or on-demand treatment for bleeding episodes only (Arm 4). Except for subjects in arm 2 who completed study after second PK assessment, subjects receiving treatment for PK assessments and/or bleeding episodes in Part A were to be entered into Part B to continue on-demand treatment for bleeding episodes for 6 additional months for a total of 12 months in the study.

The primary outcome measure was the number of subjects with "treatment success" (extent of control of bleeding episodes), which was defined as a mean efficacy rating score of <2.5 for a subject's IP-treated bleeding episodes during the study. The rate of subjects with treatment success was 100% (Clopper-Pearson exact 90% CI: 84.7 to 100.0) for bleeds where the assessments were made prospectively and excluding GI bleeds. Sensitivity analyses confirmed the results of the primary analysis.

Crossover results at 50 IU/kg VWF:RCo showed that the PK profile for rVWF (vonicog alfa) VWF:RCo was independent of administration alone or with rFVIII (ADVATE, octocog alpha) ($T_{1/2}$: 19.4 hours for rVWF and 16.6 hours for rVWF:rFVIII; IR: 1.8 U/dL per IU/kg infused for both rVWF and rVWF:rFVIII; mean residence time (MRT): 26.7 hours for rVWF and 25.2 hours for rVWF:rFVIII). FVIII levels increased substantially with a median peak at 24 hours of 111.0 U/dL for rVWF:rFVIII and 86.0 U/dL after rVWF alone, indicating that rVWF (vonicog alfa) induces a sustained increase in endogenous FVIII activity. The rVWF (vonicog alfa) PK profile was comparable at 50 IU/kg and 80 IU/kg VWF:RCo, and repeated PK at 80 IU/kg VWF:RCo showed close agreement between pretreatment and end-of-study results.

Further analysis of the PK data from the **071001** study supports the initial use of 50 IU/kg twice weekly for prophylaxis dosing in the present study for those subjects who are moving from on-demand to prophylaxis. Using 50 IU/kg for PK measurements, subjects in the **071001** study exhibiting a $T_{1/2}$ for rVWF of 14, 16, or 19 hours had rVWF plasma concentrations at 72 hours after administration of 2.55, 4.01, and 6.49% above baseline, respectively, and plasma concentrations at 96 hours after administration of 0.78, 1.40, and 2.71% above baseline, respectively. In this context it should be noted that subjects in the present study who have significant spontaneous bleeding while on twice weekly prophylaxis will have their regimen increased to 3 times per week based on clear criteria for different bleeding locations (for details see Section 8.6.4.3.1). Subjects in the present study who are switching from prophylaxis with a pdVWF product will begin on rVWF (vonicog alfa) using their same weekly total dose in IU/kg VWF:RCo used during their pdVWF prophylaxis divided into twice weekly infusions (for details see section 8.6.4.3).

A total of 125 AEs occurred in 25/37 (67.7%) subjects (62/318 infusions [19.5%]) during or after infusion with IP. Of these, 116/125 were non-serious (all mild or moderate; none were severe), and 9 SAEs were reported in 7 subjects. Of 125 total AEs, 38 were temporally associated with IP; 8 AEs were considered causally related to IP: 6 non-serious related AEs (tachycardia, infusion site paraesthesia, electrocardiogram [ECG] t-wave inversion, dysgeusia, generalized pruritis, and hot flush) occurred in 4 subjects, and 2 related SAEs (chest discomfort and increased heart rate) occurred in 1 subject. No deaths occurred during this study.

None of the subjects developed anti-VWF or anti-FVIII neutralizing antibodies and no binding antibodies to VWF or rFurin, or antibodies against CHO protein or anti-Murine IgG were observed. No clinical or subclinical signs or symptoms of a thrombogenic event were observed in this study. Following an initial increase in ultralarge VWF multimers after administration of rVWF (vonicog alfa), a notable decrease in the proportion of large VWF multimers occurred between 12 and 24 hours post infusion, due to degradation by the endogenous ADAMTS13 followed by a continued decline until the end of the 96-hour follow-up period.

Overall, the data support the safe and effective use of rVWF (vonicog alfa) with or without rFVIII (ADVATE, octocog alpha) in the treatment of bleeds in patients with VWD.

6.5.2.4 Study 071101

This was a phase 3, prospective, open-label, multicenter clinical study to evaluate efficacy and safety of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) in elective surgical procedures in adult subjects with severe VWD. A total of 24 subjects were enrolled (signed informed consent) and screened, 15 subjects were treated with rVWF (vonicog alfa), and 15 subjects completed the study.

Eleven subjects underwent a PK assessment by infusion of 50 ± 5 IU/kg rVWF:RCo at an infusion rate of up to 4 mL/min. 12 to 24 hours before surgery, subjects received a dose of 40 to 60 IU/kg rVWF:RCo. Within 3 hours prior to surgery, the subject's FVIII:C levels were assessed with a target of 30 IU/dL for minor and oral surgeries and 60 IU/dL for major surgeries. Within 1 hour prior to surgery, subjects received a dose of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) (depending on the target FVIII:C levels at the 3 hour assessment). VWF and FVIII IR and $T_{1/2}$ for each subject, when known, were used to guide the initial dose and subsequent doses.

The primary outcome measure was the overall assessment of hemostatic efficacy assessed by the investigator (hemophilia physician) 24 hours after last perioperative IP infusion or at completion of day 14 visit, whichever occurred earlier, and was summarized by the percentage of subjects in each efficacy category ("excellent", "good", "moderate" and "none"). Point estimate and corresponding 90% two-sided exact CI was calculated for the rate of subjects with an overall assessment of hemostatic efficacy. All 15 subjects treated with rVWF (vonicog alfa) (with or without ADVATE) for major (10), minor (4), and oral (1) elective surgical procedures had overall hemostatic efficacy ratings of "excellent" or "good". Most (73.3%) subjects had "excellent" overall hemostatic efficacy ratings; of these, 7 underwent major surgery and 4 underwent minor surgery. The remaining 26.7% subjects had "good" overall hemostatic efficacy ratings: 3 underwent major surgery and 1 underwent oral surgery. All 8 subjects with VWD Type 3, the subtype classified as absolute VWF deficiency, had overall hemostatic efficacy ratings of "excellent" (87.5%) or "good" (12.5%).

Intraoperative hemostatic efficacy ratings were also rated as "excellent" or "good" for all 15 treated subjects. Most (86.7%) subjects had "excellent" intraoperative hemostatic efficacy ratings; of these, 8 underwent major surgery, 4 underwent minor surgery, and 1 underwent oral surgery. Two (13.3%) subjects who underwent major surgery had "good" intraoperative hemostatic efficacy ratings. Intraoperative hemostatic efficacy was rated as "excellent" or "good" for all subjects with VWD Type 3: "excellent" for 7 (87.5%) subjects and "good" for 1 (12.5%) subject.

Only 1 subject received an intraoperative dose of rVWF (18.1 IU/kg) and ADVATE (8.1 IU/kg). The median daily postoperative weight-adjusted dose of rVWF (vonicog alfa) (with or without ADVATE) was 23.5 IU/kg on postoperative Day 1 (n=3) and 25.5 IU/kg on postoperative Day 14 (n=2). In subjects treated with rVWF:ADVATE, the daily postoperative weight-adjusted dose was 16.9 IU/kg rVWF and 7.6 IU/kg ADVATE on postoperative Day 1 (n=1) and decreased to 50.8 IU/kg rVWF and 7.6 IU/kg ADVATE on postoperative Day 7 (n=1). For subjects treated with rVWF alone, the median weight-adjusted dose (Q1, Q3) of rVWF was 35.4 IU/kg on postoperative Day 1 (n=2) and decreased to 23.7 IU/kg on postoperative Day 7 (n=4) and 25.5 IU/kg on postoperative Day 14 (n=2).

A total of 11 subjects were evaluated for PK in the study. As expected, postinfusion increases in concentrations of VWF:RCo, VWF:Ac, VWF:Ag, and VWF collagen binding (VWF:CB) were observed. Mean values for VWF:RCo were as follows: AUC0-∞/dose was 37.50 hours*IU/dL per IU/kg infused; AUC0-72h/dose was 34.08 hours*IU/dL per IU/kg infused; T1/2 was 17.83 hours; MRT was 24.32 hours; CL was 0.03117 dL/hour/kg; and volume of distribution at steady state (Vss) was 0.6837 dL/kg. Median values for VWF:RCo were as follows: AUC0-∞/dose was 32.94 hours*IU/dL per IU/kg infused; AUC0-72h/dose was 31.70 hours*IU/dL per IU/kg infused; T1/2 was 14.62 hours; MRT was 21.80 hours; CL was 0.03036 dL/hour/kg; and Vss was 0.7078 dL/kg. The VWF:RCo activity was consistent with that previously observed in clinical studies 071001 and 070701.

rVWF (vonicog alfa) was safe and well tolerated in adults with severe VWD undergoing major, minor, and oral elective surgical procedures. Of the 12 total treatment-emergent AEs (TEAEs) that occurred during the study, 2 deep vein thrombosis events (1 non-serious and 1 serious, as a part of one case) reported in one subject, who underwent total hip replacement surgery and who had concurrent condition of obesity, was assessed by the sponsor as possibly causally-related to study treatment. None of the TEAEs were either a severe allergic or hypersensitivity reaction or developed due to a severe allergic reaction.

One subject with VWD Type 3 who had an intraoperative transfusion of packed red blood cells during total knee replacement surgery tested positive for binding antibodies to VWF on postoperative Day 7 through study completion. No subjects developed neutralizing antibodies to rFVIII or binding antibodies to CHO, rFurin, or murine IgG.

In summary, the data support the safe and effective use of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) in achieving intra- and post-operative hemostasis in adult subjects with severe VWD undergoing major, minor, and oral elective surgical procedures.

6.5.2.5 Study 071401: Single Subject with von Willebrand Disease

One subject who exhibited allergic reactions to currently marketed pdVWF products was treated in the single-subject study **071401** with rVWF (vonicog alfa) only for the bleed treatment of continued hematuria, and for biopsy and surgical resection of a left-kidney mass.

For the initial rVWF (vonicog alfa) infusion, the subject received a test dose of 5% of the total dose of 60 IU/kg rVWF:RCo at an infusion rate of 1 mL/min. After a 10 to 15-minute observation period, no adverse symptoms or signs were noted and the subject received the remaining 95% of the total dose. The subject was monitored for any signs of an allergic reaction, and none were noted. Treatment with rVWF (vonicog alfa) every 12 to 24 hours was to continue at the discretion of the investigator based on VWF levels and clinical symptomatology. The subject had an excellent response and recovery, which allowed for daily dosing of rVWF (vonicog alfa) and, within 24 hours, the subject's bleeding had stopped. Daily dosing of rVWF (vonicog alfa) was maintained and the subject received his last dose on [redacted].

The subject also received rVWF (vonicog alfa) for 7 days for prophylaxis for surgery (surgical resection of a left-kidney mass). The subject experienced no hemorrhagic complications and no AEs that were considered related to the use of rVWF (vonicog alfa).

6.6 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

Current treatment of VWD patients relies on desmopressin and VWF products manufactured from pooled human plasma. Human VWF produced by recombinant technology could offer a new perspective in treatment of VWD. The benefit for the individual subject is anticipated to be significant during this clinical study. He/she may benefit from a product that minimizes excessive FVIII administration and thus allowing individualized dosing of VWF at optimal levels. Variations in VWF multimeric composition may lead to variability with respect to treating or preventing bleeds in VWD subjects, especially mucosal bleeds which are especially problematic. rVWF (vonicog alfa) product manufactured by Baxalta consistently contains ULMW VWF multimers due to the fact that the product has not been exposed to ADAMTS13.

The initial presence of these ULMW VWF multimers, which are subsequently cleaved by the subject's endogenous ADAMTS13, may result in improved platelet and collagen binding and therefore provide more predictable treatment outcomes.

By using a recombinant product, the risk of transmission of adventitious agents and other blood-borne pathogens associated with the use of products of human or animal origin has been eliminated. At this stage of product development, the key societal benefit is a better understanding of advanced treatment options for VWD and enhanced product availability.

These benefits outweigh the following identified or potential risks of rVWF (vonicog alfa):

- allergic-type hypersensitivity reactions as with any intravenous protein product
- the occurrence of thromboembolic events
- the development of neutralizing antibodies to VWF

Refer to the IB for further details on benefits and risks of the IP.

6.7 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996, with Addendum E6(R2) dated Nov 2016 EMA/CHMP/ICH/135/1995), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives 2001/20/EC and 2005/28/EC, the Declaration of Helsinki and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

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

7.2 Primary Objective

The primary objective of this study is to prospectively evaluate the 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.

7.3 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 FVIII activity

7.4 Exploratory Objectives

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

8. STUDY DESIGN

8.1 Overall Study Design

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

Subjects transitioning from on-demand treatment (OD subjects) or subjects switching from prophylactic treatment with pdVWF (pdVWF switch subjects) will receive prophylactic treatment with rVWF (vonicog alfa) for a 12-month period (up to 15 months for the qualified subjects to rollover into the continuation study, if the continuation study start up is delayed beyond the completion of subject's 12-month visit). The dose will be 50 ± 10 IU/kg rVWF twice weekly for OD subjects or will be based on their prior pdVWF dose for pdVWF switch subjects, and 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 Section 8.6.4.3).

The overall duration of prophylactic treatment with rVWF per subject will be at least 12 up to 15* months.

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 Section 8.6.4.4.2).

The overall study design is illustrated in Figure 1.

* Study treatment period is extended by 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.

8.2 Duration of Study Period(s) and Subject Participation

The overall duration of the study is approximately 27 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The subject participation period is approximately 15 to 18* months from enrollment to completion (i.e, last study visit), unless the subject is prematurely discontinued.

* Study treatment period is extended by 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.

8.3 Outcome Measures

8.3.1 Primary Outcome Measure

8.3.1.1 Efficacy

- Annualized bleeding rate (ABR) for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa)

8.3.2 Secondary Outcome Measures

8.3.2.1 Additional efficacy of Prophylactic Treatment with rVWF (vonicog alfa)

- ABR percent reduction success for OD subjects defined as at least 25% reduction of ABR for spontaneous (not related to trauma) bleeding episodes during rVWF (vonicog alfa) prophylaxis relative to the subject's own historical ABR during on-demand treatment
- ABR preservation success for pdVWF switch subjects 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 during prophylactic treatment with pdVWF
- Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 bleeding episodes during the 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
- Spontaneous ABR 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)

8.3.2.2 Safety

- AEs: incidence, severity, causality
- Thromboembolic events
- Hypersensitivity reactions
- Development of neutralizing antibodies to VWF and FVIII
- Development of total binding antibodies to VWF and FVIII

- Development of binding antibodies to CHO proteins, mouse immunoglobulin G (IgG) and rFurin
- Clinically significant changes in vital signs and clinical laboratory parameters relative to baseline

8.3.2.3 Pharmacokinetics (PK) and Pharmacodynamics (PD)

- PK parameters after a washout for on-demand subjects: incremental recovery (IR), $T_{1/2}$, 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 VWF:Rco activity, VWF:Ag, VWF:CB activity.
- PD parameters after a washout for on-demand subjects: C_{max}, T_{max}, and $AUC_{0-tlast}$ as measured in FVIII activity by the 1-stage clotting assay (FVIII:C).
- PK parameters at steady state for on-demand and switch subjects: area under the concentration versus time curve from 0 to end of the partial dosing interval ($AUC_{0-tau;ss}$), 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. PK parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.
- PD parameters at steady state for on-demand and switch subjects: $AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$ as measured in FVIII activity by the 1-stage clotting assay. PD parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.
- Time course of FVIII clotting activity (FVIII:C) levels.

8.3.3 Exploratory Outcomes Measures

8.3.3.1 [redacted]

8.3.3.2 [redacted]

8.3.3.3 [redacted]

8.3.3.4 [redacted]

8.4 Randomization and Blinding

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

8.5 Study Stopping Criteria

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 (eg, 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.

The sponsor ultimately 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.

8.6 Investigational Product(s)

8.6.1 Packaging, Labeling, and Storage

8.6.1.1 rVWF (Recombinant von Willebrand Factor, vonicog alfa)

rVWF (vonicog alfa) will be packaged in boxes with 2 glass vials, one containing the rVWF powder, and the second vial containing the diluent (water for injection). Further details are provided in the IB and Pharmacy Manual. The rVWF label will include, at a minimum, the actual VWF:RCo potency and the date of expiration.

rVWF (vonicog alfa) is a powder that should be stored refrigerated (2-8°C [36-46°F]) . Deviations from the storage condition have to be communicated and followed up with the sponsor. Inadequately stored product will have to be placed in quarantine and may only be used after written IP administration authorization by the sponsor. After removal of the product from the refrigerator the product must not be returned to the refrigerator. The reconstituted product has to be used immediately (at least within 3 hours). rVWF (vonicog alfa) must not be used beyond the expiration date printed on the vial label. Avoid freezing at all times.

8.6.1.2 rFVIII (Recombinant Factor VIII, octocog alfa /ADVATE)

ADVATE (rFVIII, octocog alfa) will be packaged in boxes with 2 glass vials, one containing the lyophilized rFVIII, and the second vial containing the diluent. Further details are provided in the IB and Pharmacy Manual. The ADVATE label will include, at a minimum, the actual FVIII:C potency and the date of expiration.

ADVATE (rFVIII, octocog alfa) should be refrigerated (2-8°C [36-46°F]) in powder form and should not be used beyond the expiration date printed on the vial.
Deviations from the storage condition have to be communicated and followed up with the sponsor. Inadequately stored product will have to be placed in quarantine and may only be used after written IP administration authorization by the sponsor. After removal of the product from the refrigerator the product must not be returned to the refrigerator and has to be used immediately. Avoid freezing at all times.

8.6.2 Reconstitution

The reconstitution procedures for both rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) products are detailed in the Pharmacy Manual.

8.6.3 Administration

Following reconstitution, rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) (in case of bleeding episode treatment) should be administered to study subjects at room temperature and within 3 hours of reconstitution. The reconstituted rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa), should be inspected for particulate matter and discoloration prior to administration, whenever the solution and container permit. The solution should be clear and colorless in appearance. If not, do not administer the product. Plastic syringes provided by the sponsor must be used since coagulation factors tend to stick to the surface of glass syringes.

Investigational product infusions should be given at a slow enough rate to ensure the subject's comfort. The rate should not exceed 4 mL/minute The investigator/ subject shall ensure that no visible residual volume remains in the syringe(s) and that the complete content is administered. Upon completion of the infusion, the butterfly catheter should be flushed with at least 2 mL of saline solution. In case of a (central) venous access device, the flush should be with at least 10 mL of saline solution. The IP infusions should be administered over a duration of 2 to 20 minutes, depending on the volume.

Only the actual potencies of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) as stated on the vial labels and described in the Pharmacy Manual should be used.

A variation of up to 10% of the intended dose for prophylactic infusions and of the intended dose for treatment of bleeding episodes is permissible and the exact dose should be recorded on the Case Report Form (CRF). Using of partial vials is not allowed.

At study visits where recovery analysis is being done, vials with the same lot numbers should be used throughout the PK IP infusion per subject.

For treatment of bleeding episodes, sequential administration will be done: separate syringes of the appropriate dose of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) will be prepared for sequential infusion. rVWF (vonicog alfa) should be infused first sequentially followed preferably within 10 minutes by infusion of ADVATE (rFVIII, octocog alfa). Only the actual potencies of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) as stated on the vial labels and described in the Pharmacy Manual should be used.

The final dose of rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) should be at a ratio of 1.3:1 ± 0.2.

8.6.4 Description of Treatment

8.6.4.1 PK-Assessment Treatment

For on-demand subjects, two PK assessments will be performed: an initial PK assessment after a wash-out period and a steady state PK assessments at the end of the study. The IP infusion for the initial PK assessment is scheduled on the baseline visit, which should be within 42 days after the completion of screening procedures and confirmation of eligibility. At the baseline visit the subjects will receive a dose of 50 ± 5 IU/kg rVWF:RCo for PK assessment. 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). A washout period of at least 5 days is required prior to infusion of rVWF (vonicog alpha) for PK assessment. The 2nd PK assessment for on-demand subjects will be performed at steady state at the end of the study(see Section 11.6). Subjects previously enrolled in rVWF studies **070701**, **071001** or **071101** and having previously undergone PK assessments in these studies are required to repeat the PK assessment due to different dose and time points used in these former studies.

For pdVWF switch subjects, two steady state PK assessments will be performed. The 1st PK will be assessed shortly after reaching steady state, which is expected to be 11 days after the 1st prophylactic dose for majority of the subjects, around the prophylactic dose #5-6. The 2nd PK will be at the end of the study. For steady state PK, 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) as long as it won't interfere with subject's the normal dosing schedule, otherwise the 96 hr sampling can be omitted (see Section 11.6). Final sample for PK analysis should be taken before next dose is administered.

8.6.4.2 Prophylaxis Initiation Treatment

The rVWF (vonicog alfa) prophylaxis initiation treatment visit will coincide with the 96 ± 2 h initial PK assessment for on-demand subjects. For pdVWF switch subjects, the rVWF (vonicog alfa) prophylaxis initiation treatment visit should occur within 42 days after the completion of screening procedures and confirmation of eligibility. At this visit subjects will receive their prophylaxis initiation dose. The prophylaxis doses are described in Section 8.6.4.3.

The subject will be trained on IP reconstitution and administration and may then qualify for home treatment (see Section 8.6.4.3.2). Refer toTable 6 (a/b) for study procedures and Table 8(a/b) for clinical laboratory assessments.

8.6.4.3 Prophylaxis Treatment

For on-demand subjects, the standard prophylactic dose is 50 ± 10 IU/kg rVWF:RCo, which may be increased up to 80 IU/kg. All on-demand subjects will initially receive rVWF (vonicog alfa) twice per week (Table 1, Schedule A). Examples of all dosing schedules are provided in Table 1.

For pdVWF switch subjects, the weekly dose (IU/kg) of IP for each patient 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 (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 (Table 1, Schedule B). A once weekly dose regimen will be allowed after switch to rVWF (vonicog alfa) only if the patient has been on a once weekly dose regimen with pdVWF.

Table 1
rVWF (vonicog alfa) Dosing Schedule Examples: Schedules A and B

Example	M	T	W	Th	F	Sat	Sun	M	T	W	Th	F	Sat	Sun
Schedule A	X				X			X				X		
Schedule B	X		X			X		X		X			X	

The prophylaxis dose may be further individualized within the range based on:

- available historical PK data
- type and severity of bleeding episodes the subject has experienced in the past and
- monitoring of appropriate clinical and laboratory measures

The individualized prophylaxic dose assignment will have to be agreed with the sponsor in advance, and the rationale should be well documented.

8.6.4.3.1 Adjustment of Dose or Dose Interval

In general, the dose and/or dose interval for each subject should not be changed unless prompted by clear medical needs. Dose and frequency adjustments should be agreed with the sponsor in advance unless it constitutes an urgent safety measure. The rationale for dosing adjustments needs to be documented in the subject's medical record.

For both OD and switch patients, dose escalations (not exceeding the upper dose limit of 80 IU/kg rVWF:RCo) and increase of dose frequency will only be allowed in case of insufficient therapeutic response with breakthrough bleeding episodes. The criteria for dose and/or frequency escalation are specific to each bleeding indication but, overall, involve 1 significant breakthrough bleeding episode despite the subject being compliant with scheduled prophylaxis treatment. For switch patients who require a dose escalation due to a breakthrough bleed, the frequency should be kept the same but the dose (IU VWF:RCo per infusion) should be increased up to 80 IU VWF:RCo. Following that, increases in frequency may be considered upon consultation with the Sponsor. For on demand subjects who require a dose escalation, at the discretion of the PI upon consultation with the Sponsor, the frequency may be kept the same but the dose (IU VWF:RCo per infusion) should be increased up to 80 IU VWF:RCo. If this proves to be insufficient, then the dosing frequency may be increased in these subjects. Table 2 presents the criteria for dosing escalation per each bleeding indication taken 50 ± 10 IU VWF:RCo/kg twice weekly dose as an example of subject's assigned starting dose.

The criteria are applicable for both OD and switch subjects who were initially assigned to twice weekly dosing. Subjects entering the study will begin prophylaxis treatment according to Schedule A (Table 1) and will remain at this dose and frequency until meeting the criteria for escalation to the next higher schedule: for example, from 2 infusions of 50 ± 10 IU VWF:RCo/kg/week to 3 infusions of 50 ± 10 IU VWF:RCo/kg/week (Schedule B) to achieve an adequate therapeutic response. If a subject started with a weekly dose (possible for switch subjects), similar criteria would apply except that the subject will be excalated to twice weekly dosing if frequency change is necessary.

Table 2
Criteria for Escalation Specific to Each Bleeding Indication

	Schedule A	Schedule B
Joint bleeding	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a spontaneous joint bleeding episode occurs while on this regimen, the subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B following its resolution	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
GI bleeding	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a severe GI bleeding episode, i.e., requiring red blood cell transfusion, occurs while on this regimen, the subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B following its resolution	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Menorrhagia	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) on days 1 and 2 of menses for 2 cycles. Menstrual flow will be monitored by the PBAC score. If the average pictorial chart score is > 185, then the subject will escalate to up to 80 IU/kg or, if necessary, to Schedule B	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) on days 1, 2, and 3 of menses. Menstrual flow will be monitored by the PBAC score.
Epistaxis	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. The subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B in the event of 1 occurrence of breakthrough bleeding requiring intervention such as iron replacement therapy, transfusion, packing, hospitalization; or 2 bleeding events that require treatment with factor replacement	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Oral and Other Mucosa	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. The subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B in the event of 1 occurrence of breakthrough bleeding requiring intervention such as iron replacement therapy, transfusion, packing, hospitalization; or 2 bleeding events that require treatment with factor replacement.	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Muscle and Soft Tissue	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a spontaneous bleeding episode occurs while on this schedule, the subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B following its resolution.	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.

Abbreviations: GI: gastrointestinal; PBAC: Pictorial Blood Assessment Chart.

If a subject does not adequately respond to rVWF (vonicog alfa) therapy, he/she will be evaluated for the presence of neutralizing and total binding anti-VWF antibodies (see Section 12.9.3.2).

If a subject experiences a bleed while receiving rVWF (vonicog alfa) three times per week, the investigator should treat the bleed with rVWF (vonicog alfa) at doses up to 80 IU VWF:RCo/kg at a frequency determined by the investigator until the bleed resolves. Upon resolution of the bleeding event, the subject will return to their assigned prophylaxis regimen.

It is essential for the success of this study that the subjects adhere to treatment regimens. Therefore, procedures for monitoring subject's compliance are implemented (see Section 10.7).

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. For example, a subject routinely infuses IP on Monday and Thursday, he/she misses the Monday time point and therefore may infuse the IP on the next day (Tuesday) and thereafter proceed with infusing the IP on Thursday (considering a minimum 12 hours between the infusions) and return to the initial schedule.

If more than 30% of infusions of IP are missed within the visit interval of 3 months the subject will be discontinued from the study (see Section 9.4).

8.6.4.3.2 General Instructions for Home Treatment for Prophylaxis

At the discretion of the investigator, a subject may be considered suitable for home treatment only after the subject has received at least 1 infusion of IP in the clinic, either during planned prophylactic IP exposure or during the treatment of bleeding episodes, and meets the following additional criteria:

1. Fully understands the concept of a clinical study and related documentation (documented training of at least 30 minutes),
2. Has a history of previous experience with home treatment including self-administration and treatment with VWF containing concentrates,
3. Has adequate time for initial training of the study drug preparation (preparation, mixing and infusion of the IP(s) (documented training of at least 30 minutes).

This applies both to subjects who were on prior on-demand treatment and to subjects switching form prophylaxis with pdVWF. In the event a healthcare professional is required to administer IP, he/she must be trained and qualified by the investigator on the above procedures prior to the decision for home treatment. A Subject Guideline detailing all instructions and information listed above will be provided to each subject.

8.6.4.4 Treatment of Bleeding Episodes

8.6.4.4.1 General Instructions for Home Treatment of Bleeding Episodes

If a subject experiences a bleeding episode, he/she should contact the study site immediately and the site investigator should provide instructions on the treatment regimen. If the subject initiates the treatment at home, he/she should at least follow up with the study site if a visit is needed as per the standard of care at the center.

In the event a healthcare professional is required to administer treatment at the subject's home, he/she must be trained and qualified by the site investigator on the above procedures prior to the decision for home treatment. Once a subject has received 1 infusion of rVWF (vonicog alfa) in the clinic (either during planned IP exposure or during the treatment of a bleeding episode) and meets the criteria for home treatment, the treatment of bleeding episodes with IP can be conducted at home (see Section 8.6.4.3.2).

If a subject is not qualified for home treatment, rVWF (vonicog alfa) infusions must be administered at the study site.

If a subject experiences a bleeding episode that requires treatment between the screening and the prophylaxis initiation visit, the subject will be treated with IP (rVWF with or without ADVATE). Treatment with IP must occur at the study site unless the subject has previously qualified for home treatment with rVWF (vonicog alfa). If rVWF (vonicog alfa) treatment is not feasible, the subject may use his/her standard of care, such as commercial pdVWF/FVIII products. In any case a washout period of at least 5 days is required prior to rVWF (vonicog alfa) PK infusion at the initial PK assessment visit for on-demand subjects.

If a subject experiences a bleeding episode requiring treatment during the PK assessment, rVWF (vonicog alfa) should be used to treat the bleed. Blood draws for PK assessment will be stopped and the PK assessments will be repeated once the bleed has resolved and the subject is free of any symptoms related with the bleeding episode. Dose and frequency of rVWF (vonicog alfa) infusions or any other replacement therapy to stop the bleed should be recorded in the electronic Case Report Form (eCRF), and the reason for the use of any non-IP product or therapy should be documented.

8.6.4.4.2 Dosing Recommendations for Treatment of Bleeding Episodes

If an acute bleeding episode occurs, the subject will be treated with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa). It is the sponsor's opinion that, in many cases, treatment with ADVATE (rFVIII, octocog alfa) may not be necessary, since rVWF (vonicog alfa) prophylaxis will serve to increase endogenous FVIII levels. However, if endogenous FVIII is below 30-40 % or is unknown and cannot be estimated from the subject's PK study, an infusion of rVWF: ADVATE at an rVWF: ADVATE ratio of 1.3:1± 0.2 should be administered initially. Subsequent infusions should be with rVWF:RCo 40 to 60 IU/kg with or, in many cases,without 30 to 45 IU/kg ADVATE (only to be administered if plasma FVIII levels fall below 30 IU/L during the treatment period). Dosing may be adjusted downward or upward up to 80 IU/kg rVWF at the treating physician's discretion based upon the subject's prior history, PK and other factors.

If FVIII levels are not available, dosing is at the discretion of the investigator based upon the individual subject's PK data. Using ADVATE (rFVIII, octocog alfa) in addition to rVWF (vonicog alfa) in subsequent doses carries the risk of an excessive rise in FVIII:C. Therefore, reduced doses of ADVATE (rFVIII, octocog alfa) and/or prolongation of the dose interval should be considered.

The following is general guidance and the sponsor's suggestion for treatment of breakthrough bleeds, however each PI will determine the treatment based on the local acceptable practice how to monitor and adjust treatment for a bleeding episode. An effort should be made to discuss with the sponsor (or sponsor's delegate) the treatment strategy.

In general the aim of the initial dose should be full replacement of VWF with VWF:RCo levels of >0.6 IU/ml (60%) and FVIII:C of >0.4 IU/mL (40%). In major bleeding episodes, subsequent doses should keep the trough level of VWF:RCo >50% for 3 days and then as deemed necessary by the investigator for subsequent days. In moderate bleeding episodes, the dose and trough level may be reduced to >30% for as long as deemed necessary by the investigator. Treatment for minor bleeding episodes will generally consist of only 1 or 2 doses of rVWF (vonicog alfa) IP.

If the VWF:RCo level is above 150%, a planned treatment should be delayed by at least 12 hours; if the VWF:RCo level is above 200%, a planned treatment should be delayed by at least 24 hours. In either case, a lower subsequent dose (e.g., 20 IU/kg VWF:RCo) may be appropriate.

Dosing recommendations are listed in Table 3.

Dosage must be individualized based on the subject's weight, VWD type, and the severity of the bleeding episode, as well as on monitoring of appropriate clinical and laboratory measures. In the phase 1 study **070701**, 1.0 IU/kg VWF:RCo raised the circulating level of VWF:RCo by 0.017 IU/mL (1.7 %). In the same study, the observed mean half-life for rVWF (vonicog alfa) was 19.3 hours, with a standard deviation of 10.9 hours.

Table 3
rVWF:RCo Dosing Recommendations for the Treatment of Bleeding Episodes Due to VWD

Classification of VWD	Hemorrhage	Dosage (IU VWF:RCo/kg BW)
Type 1 • Severe (Baseline VWF:RCo activity typically <20%)	Minor (e.g., epistaxis, oral bleeding, menorrhagia[a])	40 to 50 IU/kg (1 or 2 doses)
	Major (e.g., severe or refractory epistaxis, menorrhagia*, GI bleeding, CNS trauma, hemarthrosis, or traumatic hemorrhage)	Initial dose 50 to 75 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment
Type 2 (all variants) and Type 3	Minor (clinical indications above)	40 to 50 IU/kg (1 or 2 doses)
	Major (clinical indications above)	Initial dose of 60 to 80 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment

[a] Menorrhagia is defined as excessive bleeding during menstruation. A diagnosis of menorrhagia will be defined by a prospectively completed Pictorial Blood Assessment Chart (PBAC) score >185 and normal cervical cytology or requiring use of a VWF-containing concentrate for treatment of excessive menstrual bleeding for at least one menstrual cycle during the prior year.

Variances of up to 10% in dosing are permissible during treatment of bleeding episodes, but rounding to the nearest vial size should be avoided.

Subjects with non-neutralizing binding anti-VWF antibodies should initially be treated with a dose known to be efficacious based on the subject's medical treatment history which may differ from the recommendations provided in Table 3. Subjects should be monitored for lack of efficacy as well as for FVIII (mandatory), VWF:RCo (mandatory), and VWF:Ag (optional where testing is not available) levels after 3 to 6 hours. Re-dosing with rVWF (vonicog alfa) in combination with ADVATE (rFVIII, octocog alfa) using the same (initial) dose and adaptation of the dosing frequency should be considered until cessation of the bleed, if the FVIII and/or VWF:RCo levels drop below 30%-50% depending on bleeding severity.

The number of subsequent infusions and the dosage levels prescribed will be determined by the investigator on the basis of the clinical severity, response to current therapy, available laboratory data, and the subject's historical treatment for similar bleeding episodes.

8.6.4.5 Treatment of Surgical Bleeding

Subjects enrolled in this study who require surgery or dental procedures will be treated with IP to manage their surgical bleeding then afterwards will resume their prophylactic rVWF (vonicog alfa) treatment schedule. Subjects who at time of screening have an already scheduled surgical intervention are not eligible for participation in the study.

8.6.4.5.1 Major, Minor and Oral Surgery Definition

The following definitions and criteria are used to serve as a guidance for *major, minor and oral surgery*.

Major surgeries generally refer to major orthopedic surgery (e.g., joint replacement, arthroscopic or open synovectomy, arthrodesis, hardware removals like plates or intramedullary nails, etc.), major abdominal surgery (e.g. open or laparoscopic hernioplasty, cholecystectomy, colon or small bowel resection, etc.), major gynecological surgery (e.g. open or laparoscopic myomectomy, hysterectomy, removal of endometriosis, polyps, cysts, adhesiolysis, etc.), major head and neck surgery (e.g.: tonsillectomy, adenoidectomy, rhinoplasty, lymphadenectomy, thyroidectomy, parotidectomy. etc.), any intracranial , cardiovascular or spinal surgery and any other surgery which has a significant risk of large volume blood loss or blood loss into a confined anatomical space. Extraction of impacted third molars is generally also considered major surgery due to the expected difficulty of surgery and the expected blood loss.

Minor surgeries generally refer to interventions such as placement of intravenous access devices, removal of small skin lesions, arthroscopy, gastroscopy, colonoscopy or conisation.

Oral surgeries comprise extractions of fewer than three teeth, if the teeth are non-molars and have no bony involvement.

A summary schedule of visit assessments and laboratory sampling is included in Supplement tables in Section 20.2.1 and Section 20.3.1.

8.6.4.5.2 Preoperative Priming Dose

12- 24 hours prior to surgery, a priming dose with rVWF (vonicog alfa), using the rVWF IR and $T_{1/2}$ for this subject , will be infused to allow the endogenous FVIII levels to raise to at least 30 IU/dL (minor, oral surgery), or 60 IU/dL (major surgery) at the time of the loading dose of rVWF (vonicog alfa) is infused.

As a general guidance a priming dose of 40-60 IU/kg rVWF:RCo will be administered. If not assessed prior to the preoperative priming dose, a IR recovery may be calculated for subjects undergoing minor and oral surgery.

8.6.4.5.3 Preoperative Loading Dose

An rVWF (vonicog alfa) loading dose should be administed within 3 hours before surgery. VWF and FVIII levels should be assessed within 3 hours prior to surgery initiation and results must be available prior to administering the loading dose. If FVIII levels prior to loading dose administration are not at least 30 IU/dL (minor, oral surgery), or 60 IU/dL (major surgery) ADVATE (rFVIII, octocog alfa) will be administered in addition to rVWF (vonicog alfa) in order to raise FVIII:C levels to recommended levels.

The preoperative loading dose will be calculated as the difference in the target peak and baseline plasma VWF:RCo levels divided by the IR (ΔVWF:RCo x BW (kg) /IR). The PK results will be provided prior to the planned surgery. If the IR is not available, assume an IR of 1.7 IU/dL per IU/kg and calculate the initial dose as follows: (100 − baseline plasma VWF:RCo) x BW (kg) / 1.7. For minor and oral surgery, the IR from the Preoperative Priming Dose visit will be used to guide dosing and the target peak is 50-60 IU/dL VWF:RCo and 40-50 IU/dL FVIII. For major surgery, the target peak is 100IU/dL VWF:RCo and 80-100 IU/dL FVIII.

The surgery may only start after normalization of the activated partial thromboplastin time (aPTT).

8.6.4.5.4 Intra- and Postoperative (maintenance) Dosing

After the preoperative loading dose(s), subjects who have not achieved the desired postinfusion recovery will continue to receive rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) as a bolus infusion, depending on VWF and FVIII levels. The peri- and post-operative substitution regimen will be individualized according to the PK results, intensity and duration of the hemostatic challenge, and the institution's standard of care.

Subjects undergoing minor surgery will be infused with rVWF (vonicog alfa) every 12-24 hours or every other day, targerting ≥30IU/dL (rVWF and FVIII) for at least the first 48 hours.

Subjects undergoing oral surgery will be infused with rVWF (vonicog alfa) at least once within the first 8-12 hours, targeting ≥30 IU/dL (rVWF and FVIII).

Subjects undergoing major surgery will be infused with rVWF (vonicog alfa) every 12-24 hours for at least the first 72 hours post-surgery, targeting a VWF:RCo and FVIII:C trough plasma level >50 IU/dL, followed by further treatment post-72 hours for as long as deemed necessary by the Investigator, targeting a VWF:RCo and FVIII:C trough plasma level of ≥30 IU/dL.

Dose modifications based on pre-infusion VWF/FVIII levels will be performed as needed. For subsequent infusions post surgery, in case pre-infusion levels are not available prior to the consecutive infusion in a timely manner, pre-infusion levels from the previous dose may be used by the investigator for dosing guidance.

Peak plasma level guidance is matching to Section 8.6.4.4.2

A schedule of all perioperative visit assessments and laboratory sampling can be found in supplement tables in Section 20.2.1 and Section 20.3.1.

8.6.4.6 Thrombosis Prophylaxis

Thromboembolic events have been reported in patients who have VWD, especially in the setting of known risk factors for thrombosis including low ADAMTS13 levels. Therefore, subjects who are at risk for developing thromboembolic events should be monitored for early signs of thrombosis, and prophylaxis measures against thromboembolism should be instituted according to current recommendations and standard of care. For all subjects who are VWD patients and are receiving VWF concentrate, attention should be given to avoid exceeding maximal recommended plasma activity levels of VWF:RCo (250 IU/dL) and FVIII (250 IU/dL).

Anticoagulation measures, such as heparin, are acceptable and should follow study site standards. The investigator will record the use and reasons for such measures/agents on the appropriate CRF.

8.6.5 Investigational Product Accountability

The investigator will ensure that the IP(s) is stored as specified in the Pharmacy Manual and that the storage area is secured, with access limited to authorized study personnel. All temperature excursions at the subject's home need to be monitored by the site (please refer to the pharmacy manual). The investigator will maintain records that the IP(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. The IP(s) must be dispensed only at the study site or other suitable location (e.g., infusion center; home, as applicable per study design), as specified in the protocol (see Section 10). Records will be maintained that includes the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

8.7 Source Data

Per ICH E6(R2) on GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). These may be in paper and/or electronic format. Source documents for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

No data will be entered directly onto the CRF.

For additional information on study documentation and CRFs refer to Section 17.2. The use of subject diaries is described in Section 10.5.

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding
   a. Type 1 (VWF:RCo <20 IU/dL) or,
   b. Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2M or,
   c. Type 3 (VWF:Ag ≤3 IU/dL).
2. Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.
3. For on-demand patient group, subject currently receiving on-demand treatment for whom prophylactic treatment is recommended by the investigator.
4. For pdVWF switch patient group, subject has been receiving prophylactic treatmentof pdVWF products for no less than 12 months prior to screening.
5. For on-demand patient group, subject has ≥3 documented spontaneous bleeds (not including menorrhagia) requiring VWF treatment during the past 12 months.
6. Availability of records to reliably evaluate type, frequency and treatment of bleeding episodes during at least 12 months preceding enrollment. Up to 24 months retrospective data should be collected if available. Availability of dosing and factor consumption during 12 months (up to 24 months) of treatment prior to enrollment is required for pdVWF switch subjects and is desired (but not a requirement) for on-demand subjects.
7. Subject is ≥18 years old at the time of screening and has a body mass index ≥15 but <40 kg/m^2.
8. If female of childbearing potential, subject presents with a negative blood/urine pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.[i]
9. Subject is willing and able to comply with the requirements of the protocol.

[i] Refer to Section 20.4 for a list of adequate contraceptive methods for females of childbearing potential.

9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

1. The subject has been diagnosed with Type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD (eg qualitative and quantitative platelet disorders or prothrombin time (PT)/international normalized ratio [INR] >1.4).
2. The subject is currently receiving prophylactic treatment with more than 5 infusions per week.
3. The subject is currently receiving prophylactic treatment with a weekly dose exceeding 240 IU/kg.
4. The subject has a history or presence of a VWF inhibitor at screening.
5. The subject has a history or presence of a FVIII inhibitor with a titer ≥0.4 Bethesda units (BU) (by Nijmegen modified Bethesda assay) or ≥0.6 BU (by Bethesda assay).
6. The subject has a known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins.
7. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
8. The subject has a medical history of a thromboembolic event.
9. The subject is human immunodeficiency virus (HIV) positive with an absolute Helper T cell (CD4) count <200/mm^3.
10. The subject has been diagnosed with significant liver disease per investigator's medical assessment of the subject's current condition or medical history or as evidenced by any of the following: serum alanine aminotransferase (ALT) greater than 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).
11. The subject has been diagnosed with renal disease, with a serum creatinine (CR) level ≥2.5 mg/dL.
12. The subject has a platelet count <100,000/mL at screening.
13. The subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to signing the informed consent.

14. The subject is pregnant or lactating at the time of enrollment.
15. Patient has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
16. The subject has participated in another clinical study involving another IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
17. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
18. The subject is scheduled for a surgical intervention.
19. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
20. The subject has a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
21. The subject is in prison or compulsory detention by regulatory and/or juridical order.
22. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.

9.3 Delay Criteria

1. If the subject has an acute bleeding episode or presents with an acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) the screening visit will be postponed until the subject has recovered.

9.4 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (i.e., reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the termination visit (including cases of withdrawal or discontinuation) are described in Section 10.6 and Section 20.2.

Discontinuation (i.e., complete withdrawal from study participation) may be due to dropout (i.e., active discontinuation by subject) or loss to follow-up (i.e., discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also will be withdrawn from treatment or discontinued from further study participation for the following reasons:

1. The subject is scheduled for an extended treatment period >3 months with non-topical immunomodulating drugs other than anti-retroviral chemotherapy (e.g., α-interferon, corticosteroid agents [equivalent to hydrocortisone greater than 10 mg/day]) during the course of the study.
2. Subjects with chronic hepatitis B or C develop ALT/AST levels exceeding 5 times the ULN for >1 month.
3. Subjects who experience severe hypersensitivity reactions, e.g., anaphylaxis upon exposure to rVWF (vonicog alfa).
4. Subjects who develop a neutralizing inhibitor to rVWF (vonicog alfa) and/or ADVATE (rFVIII, octocog alfa) (biological assays) that results in significant clinical effect, including but not limited to increasing the weekly dose of rVWF by $\geq$ 50%.
5. Subjects who demonstrate clinical signs of thromboembolic events.
6. The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through completion of the pregnancy and up to 1 year post delivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome.
7. The subject begins lactating. IP exposure will be discontinued. The investigator will record a narrative description of the course of the baby's development.
8. The subject is not compliant with the prophylactic treatment regimen and does not adhere to the frequency of IP administration. Once >30% of infusions are missed within a visit interval (3 months), the subject will be discontinued from further participation in the study.
9. The subject repeatedly uses other VWF products for prophylaxis or for the treatment of bleeding episodes in the absence of an acceptable justification to the sponsor.

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient who provides informed consent (i.e., signs and dates the informed consent form) is considered a subject enrolled in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (e.g., 071301) to be provided by the sponsor, 2- or 3-digit number study site number (e.g., 02) to be provided by the sponsor, and 3- or 4-digit subject number (e.g., 0003) reflecting the order of enrollment (i.e., signing the informed consent form). For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 071301-020003. All study documents (e.g., CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The study site is responsible for maintaining a screening log that includes all subjects who provided informed consent. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRF, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

The overall study design is illustrated in the Figure 1. Details on the procedures to be performed at each study visit, including screening, are provided in Supplement 20.2 „Schedule of Study Procedures and Assessments“ and Supplement 20.3 „Clinical Laboratory Assessments“.

10.3.1 Screening Visit

Written informed consent must be obtained from each subject before any study related procedures are performed. To initiate screening procedures, at least 72 hours must have elapsed since the last VWF administration for on-demand subjects and the subject must not be actively bleeding at the time of screening. For switch subjects, the usual interval between their pdVWF prophy infusions must have elapsed since the last VWF administration and the subject must not be actively bleeding at the time of screening. Multimer analysis and VWD gene mutation analysis should be performed at screening if not available in the subject's medical history.

The screening visit will be delayed if the subjects presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like symptoms, inflammatory diseases) until the event has resolved. All screening procedures and confirmation of eligibility shall take place within 42 days prior to the first infusion of IP. If the IP is not infused within 42 days, all screening assessments except blood group, human leukocyte antigen (HLA), genetics, multimeric pattern and [redacted], must be repeated to reconfirm eligibility. Refer to Supplement 20.2 and Supplement 20.3. Upon completion of screening procedures, subject eligibility will be confirmed by the sponsor on a subject eligibility form before additional study procedures are undertaken. The subject will maintain a diary that will include infusion logs (see Section 10.5). The allocation of IP will be initiated after the subject has qualified for home treatment (see Section 8.6.4.3.2).

In the event of a subject experiencing a bleeding episode that requires treatment between the screening visit and the subsequent visit (i.e. initial PK assessment visit for on-demand subjects or prophylaxis initiation visit for switch subjects), the subject will be treated with rVWF (vonicog alfa). If rVWF (vonicog alfa) is not available for any reason, e.g., subject not yet trained on IP administration, study site visit for IP administration not feasible, etc., the subject may use his/her standard of care, such as commercial pdVWF/FVIII products, and the reason for the use of non-IP products should be clearly documented.

10.3.2 Baseline Visit – Initial PK Assessment (On-demand Subjects Only)

After screening and confirmation of eligibility on-demand subjects will undergo an initial PK assessment. Subjects will receive a dose of 50 ± 5 IU/kg rVWF:RCo to determine VWF and FVIII levels. 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). See Section 20.2 and Section 20.3. IP infusion vials from the same lot number should be used for all PK-assessments per subject. Samples for measurement of FVIII and VWF activity taken through to 6 hours post-infusion will be obtained from an extremity different from that used for the infusion of IP. Where needed, the phlebotomy site will be kept patent via an infusion of normal saline. In this event, at least 5 mL of blood will be collected and discarded before collection of the next test sample into a fresh syringe.

If the subject has a central venous catheter, the central line should be used to administer the infusion and a peripheral venipuncture should be used to collect the blood samples.

In the event that a blood sample must be drawn through the central line used for administration of IP, the line must first be flushed with at least 10 mL normal saline or other suitable catheter flush solution that does not contain anticoagulant. At least 5 mL of whole blood must be collected and discarded prior to obtaining the sample.

If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.6.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment.

For pdVWF switch subjects, PK profile will not be assessed until reaching steady state after initiation of prophylaxis (see Section 10.3.4).

10.3.3 Prophylaxis Initiation Visit

The prophylaxis initiation visit will occur after the blood sample for the 96 hour PK assessment is drawn for on-demand subjects or within 42 days after screening and confirmation of eligibility for pdVWF switch subjects. The subject will receive the first rVWF (vonicog alfa) prophylactic dose of rVWF: RCo. Details on dose are provided in Section 8.6.4.3.

Procedures and assessments at this visit include (but are not limited to): AEs, bleeding episodes, medications taken, and non-drug therapies. Within 2 hours prior the IP infusion, a physical examination will be performed. Vital signs will be assessed within 30 minutes prior to IP rVWF (vonicog alfa) infusion and 30 minutes ± 15 minutes after IP infusion. Further details are provided in Supplement 20.2 and Supplement 20.3.

10.3.4 Initial Steady State PK-Assessment (pdVWF switch subjects only)

For pdVWF switch subjects, a full PK profile will be assessed at steady state conditions on two occasions. The initial PK assessment will be performed shortly after reaching steady state after starting prophylaxis dosing, which is suggested after 11 days post the 1st, around prophylaxis dose #5-6. The 2nd PK assessment at steady state will be performed at the end of the study.

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). In case the dosing schedule does not permit the 96 hr sampling, this sampling time point can be omitted (See Section 11.6). IP infusion vials from the same lot number should be used for all PK-assessments per subject.

Samples for measurement of FVIII and VWF activity taken through to 6 hours post-infusion will be obtained from an extremity different from that used for the infusion of IP. Where needed, the phlebotomy site will be kept patent via an infusion of normal saline. In this event, at least 5 mL of blood will be collected and discarded before collection of the next test sample into a fresh syringe.

If the subject has a central venous catheter, the central line should be used to administer the infusion and a peripheral venipuncture should be used to collect the blood samples. In the event that a blood sample must be drawn through the central line used for administration of IP, the line must first be flushed with at least 10 mL normal saline or other suitable catheter flush solution that does not contain anticoagulant. At least 5 mL of whole blood must be collected and discarded prior to obtaining the sample.

If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.6.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment. In case of surgery or bleeding, the PK assessment should be performed after 11 days after 1st prophylactic dose after re-start of prophylactic regimen. See section 11.6 for more details.

10.3.5 Treatment of Bleeding Episodes

Treatment of bleeding episodes is described in detail in Section 8.6.4.4 and treatment of perioperative bleeding is described in detail in Section 8.6.4.5.

10.3.6 Perioperative Visits (only applicable if surgery is needed)

The perioperative visits from priming dose through postoperative day 14 will be required to check daily intra- and postoperative weight-adjusted dose of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa). Details on the procedures and assessments performed at each visit can be found in supplement tables in Section 20.2.1 and Section 20.3.1.

10.3.7 Follow-Up Visits

Visits will be performed after the prophylaxis initiation visit at 1 month ± 1 week, 2 months ± 1 week, and 3 months ± 2 weeks and thereafter every three months ± 2 weeks. Additional visits may occur if clinically indicated (see Section 10.3.8).

When possible, site visits should be scheduled on days when the subject is expected to infuse rVWF (vonicog alfa). Within 2 hours prior to the rVWF (vonicog alfa) IP infusion, a physical examination will be performed. Vital signs will be assessed within 30 minutes prior to IP infusion and 30 minutes ± 15 minutes after IP infusion. Incremental recovery (IR) will be determined at each follow-up visit based on VWF:RCo activity assessed prior to and after IP infusion.

The blood sample for IR analysis will be drawn within 30 minutes prior to IP infusion and 30 minutes ± 5 minutes after IP infusion. rVWF (vonicog alfa) will be infused at the regular prophylactic dose. For each subject's recovery analysis IP infusion, vials from the same lot number should be used.

Testing for VWF:RCo VWF:CB, rVWF:Ag, and FVIII:C level will be performed using the blood sample obtained before and after IP infusion.

The blood sample prior to IP infusion will also be used for the assessment of neutralizing and binding antibodies, clinical chemistry and hematology. For on-demand subjects, a washout period of at least 72 hours after the last infusion applies before the blood draw for the immunogenicity assays. For switch subjects, the wash out period may be reduced to the time interval between their pdVWF prophy infusions Bleeding episodes and the hemostatic efficacy will be evaluated based on the review of the patient diary. See Section 20.2 and Section 20.3. The evaluation of IP consumption and treatment compliance will be performed based on subject's diary entries. If a subject is not compliant with the prophylactic treatment regimen and does not adhere to the required frequency of administration of IP infusions (>30% of infusions were missed within a visit interval [3 months]) the subject will be withdrawn from the study.

At the 6 months ± 2 week visit an ECG will be performed and [redacted] data will be collected.

For the hemostatic efficacy assessment the following information will be recorded by the subject in the patient diary: bleeding location, type, severity, onset and resolution date and time, infusion date and time, clinical efficacy according to the rating scale. If at any time during the study a subject's bleeding episode does not adequately respond to rVWF (vonicog alfa) therapy, he/she will be evaluated for the presence of neutralizing and total binding antibodies. Refer to Section 12.9.3.2.

Further guidance on completing the subject's diary will be provided to the subjects during training for home treatment (see Section 8.6.4.3.2).

10.3.8 Unscheduled Visits

For any unscheduled visit (except for collection of IP) a clinical assessment will be performed as per the scheduled follow-up visits with the exception of [redacted], ECG, and IR determination (refer to Supplement 20.2 and Supplement 20.3).

Subjects who have more than one bleeding episode in 3 months, or an increased frequency of bleeding, should go to the study site for an unscheduled visit.

Follow-up visits after the subject has experienced a bleed may be requested by the investigator. Additional assessments may be required which are at the discretion of the investigator.

10.3.9 End of Study PK Assessment and Study Termination Visit

At the 12* month ± 2 week visit, a full PK analysis at steady state will be performed for both cohorts: on-demand and switch subjects. 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) unless dosing schedule does not permit, in which case the 96 hr sampling can be omitted. If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.6.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment and the PK assessment should be performed after 11 days after 1st prophylactic dose after re-start of prophylactic regimen. See section 11.6 for more details.

Refer to Supplement 20.2 and Supplement 20.3 for the other assessments to be performed at the PK assessment and study completion visits.

For on-demand subjects, a washout period of at least 72 hours is required between the PK infusion and the study termination visit (at the time of the 96 hour postinfusion PK assessment). For switch subjects, the wash out period may be reduced to the time interval between their rVWF (vonicog alfa) prophy infusions.Refer to Supplement 20.2 and Supplement 20.3 for the list of assessments to be performed at the termination visit.

Subjects will be offered the option to continue to receive rVWF (vonicog alfa) in a long-term continuation study*.

* Study treatment period is extended by 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.

For subjects whose completion date is extended beyond the 12-month visit due to delay in continuation study start-up, the 12-month ± 2 weeks visit will be considered as a follow-up visit, and EOS visit will be performed once the subject can rollover into the continuation study, from 12 month ± 2 weeks to 15 month ± 2 weeks post prophylaxis initiation visit, as applicable.. Both the 12-month ± 2 weeks visit rescheduled as a follow-up visit, and the rescheduled EOS visit will be recorded in the CRF.

10.4 Medications and Non-Drug Therapies

The following medications and non-drug therapies are **not** permitted within 30 days before study entry and during the course of the study:

Medications:

- 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) and an extended treatment period >3 months.
- Another investigational and/or interventional study drug (except rVWF and FVIII administered under the surgery protocol).

A subject who has taken any of these medications or received any of these non-drug therapies during the study will be withdrawn from the study.

The following medications are permitted during the course of the study:

- Antifibrinolytics (e.g., tranexamic acid, ε-amino caproic acid) or topical hemostats as needed, according to each institution's standard of care. These may be used, in accordance with local standard clinical practice, as the initial or only treatment for minor and moderate bleeding events. However, if the bleeding has not stopped within 24 hour following administration of this non-VWF treatment, infusion(s) with rVWF (vonicog alfa) should be started per protocol
- Emergent use of a VWF concentrate other than rVWF (vonicog alfa) may be permissible under certain circumstances (see Section 8.6.4.4.1)

Details of all adjunctive hemostatic medication used, including dose and reason for use, must be recorded in the eCRF.

10.5 Subject Diary

An electronic subject diary will be provided to each subject at the screening visit to record the following information:

1. IP infusions to include date, start and stop times of the infusion, number of vials utilized, and infusion volume for prophylactic treatment or treatment of spontaneous and traumatic bleeding episodes
2. Details of bleeding episodes (site, type, severity and date/time of bleeding) and response to treatment as described in Section 8.6.4.4
3. Subjective hemostatic efficacy assessments
4. Untoward events/unwanted experiences
5. Concomitant medications (including immunizations) and non-drug therapies
6. Patient Reported Outcomes (PROs)

Subjects and/or their legally authorized representatives will be trained on use of the diary. The diary will be provided in electronic format and remain with the subject for the duration of the study. The investigator will review the diary for completeness and request missing information periodically and in a timely manner. The investigator will record/capture any unwanted experience reported by the subject which may qualify as an AE on the AE eCRF.

Infusions performed at the study site will first be recorded in the site's source documents and not in the patient diary.

Subject entries in the diary will serve as source records. During study participation the investigator has access to the database holding the subject diary data. After study closure, the investigator will receive the diary records for their subjects, including audit trail records, in PDF format. The data will be transmitted to the CRF by a validated transfer.

Paper diary may be utilized in rare case where electronic diary use is not possible.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have completed all study procedures according with the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, AE (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, e.g., technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the study termination visit. If the termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the termination visit.
If a subject terminates participation in the study and does not return for termination visit, his/her last recorded assessments shall remain with the last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.2 Schedule of Study Procedures and Assessments and Supplement 20.3 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

10.7 Procedures for Monitoring Subject Compliance

Subject compliance with the procedures of this study (treatment regimens and study visits) will be monitored by the investigator or/a licensed healthcare professional at the study site.

During the regular scheduled follow-up visits a direct review of the subject's source data (e-diaries) will be performed at the sites and evaluated against the protocol requirements. In addition drug accountability will be evaluated at each follow-up study visit and the study termination visit by comparing the infusions recorded in the subject diary with empty vials returned by each subject to the study site, and the study site's dispensing record. Protocol deviations will be noted in the final report.

11. ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

11.1 Assessment of Spontaneous Bleeding Episodes/Annualized Bleed Rate

The annualized bleed rate (ABR) will be assessed based upon each individual spontaneous bleed, requiring coagulation factor replacement therapy, i.e., rVWF (vonicog alfa) treatment. The following details on bleeding episodes will be recorded by the subject in the electronic diary (for home treatment), the subject's healthcare provider in the site's source documents (for treatments away from the primary investigative site), or by authorized, qualified personnel at the participating site in the subject's medical records (for hospital-based treatment):

- Location of bleed; i.e., joint, menorrhagia, epistaxis, gastrointestinal, soft tissue, muscle, body cavity, intracranial, etc.
- Type of bleed; i.e., spontaneous, traumatic, unknown
- Severity of bleed; i.e., minor, moderate, and major (see Table 3)
- Date and time of onset of bleed
- Date and time of each infusion of rVWF (vonicog alfa) or rVWF (vonicog alfa)-ADVATE (rFVIII, octocog alfa) used to treat a bleeding episode
- Date and time of resolution of the bleeding episode

Study site personnel are qualified after they have undergone training during the qualification of the site.

All types of bleeds, including traumatic bleeds, will be recorded. Bleeding episodes should be organized by where they occur in addition to whether they occurred spontaneously or due to a traumatic event.

Bleeds occurring at the same anatomical location (e.g., right knee) with the same etiology (i.e., spontaneous versus injury) within 24 hours after onset of the first bleed will be considered a single bleed. Bleeding occurring at multiple locations related to the same injury (e.g., knee and ankle bleeds following a fall) will be counted as a single bleeding episode.

All efforts should be made to use rVWF (vonicog alfa) for treatment of bleeding episodes. If needed, the use of a VWF concentrate other than IP for the treatment of bleeding episodes will not disqualify the subject from further participation in the study.

11.2 Evaluation of ABR Before rVWF Prophylaxis and ABR Under rVWF Prophylactic Treatment

At screening, the subject's medical history will be recorded, including the number and location of all spontaneous and traumatic bleeding episodes within the past 12 months (up to 24 months if available). The maximum interval of bleed-free periods as well as trauma induced bleeding episodes will also be recorded (prospectively and retrospectively).

11.3 Number of Infusions and Total Weight Adjusted Consumption of rVWF and ADVATE and historical prophylaxis dosing and factor consumption during pdVWF prophylaxis treatment prior to enrollment

The number of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) (in case of bleeding episode treatment) infusions will be logged in the subject diary. Based on these entries the weight adjusted consumption will be calculated.

At the screening, historical pdVWF dosage and dosing frequency during 12 and up to 24 months of pdVWF prophylactic treatment prior to enrollment will be recorded for the pdVWF switch subjects in order to calculate the consumption of pdVWF.

11.4 Assessment of Efficacy for Treatment of Bleeding Episode

Investigators will be asked to assess and record hemostatic efficacy after resolution of each bleeding episode using the 4-scale rating system outlined in Table 4.

Table 4
Efficacy Rating Scale

Rating	Efficacy Rating Criterion	
	Minor and Moderate Bleeding Events	**Major Bleeding Events**
Excellent (=1)	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF containing coagulation factor containing product required	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF containing coagulation factor containing product required
Good (=2)	1-2 infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required	< 1.5 x infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required
Moderate (=3)	3 or more infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required	≥ 1.5 x infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required
None (=4)	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF containing coagulation factor containing product required	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF containing coagulation factor containing product required

11.5 Assessment of Efficacy for Treatment for Surgical Bleeding

For those undergoing surgery, the operating surgeon will be asked to assess and record actual versus predicated blood loss and intraoperative hemostatic efficacy immediately after surgery.

The investigator will be asked to assess and record an overall assessment of hemostatic efficacy 24 hours after the last perioperative rVWF (vonicog alfa) infusion or at day 14 post-operation, whichever occurs first, using the 4-scale rating system described in Table 5.

Table 5
Assessment of Hemostatic Efficacy

Rating	Overall Assessment of Hemostatic Efficacy 24 Hours After the Last Perioperative rVWF Infusion
Excellent (1)	Intra- and post-operative hemostasis achieved with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) was as good or better than that expected for the type of surgical procedure performed in a hemostatically normal subject
Good (2)	Intra- and post-operative hemostasis achieved with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) was probably as good as that expected for the type of surgical procedure performed in a hemostatically normal subject
Moderate (3)	Intra- and post-operative hemostasis with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) was clearly less than optimal for the type of procedure performed but was maintained without the need to change the rVWF (vonicog alfa) concentrate
None (4)	Subject experienced uncontrolled bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of rVWF (vonicog alfa) concentrate

11.6 rVWF Pharmacokinetics and Pharmacodynamics

PK will be assessed twice for all subjects.

For on-demand subjects, an initial PK assessment using a dose of 50 IU ± 5 IU/kg rVWF:RCo will be performed at the baseline visit, and 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 week 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 assay. 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 assessment using the subject's individualized dose will be performed shortly after reaching steady state, which is estimated to be reached for the majority of subjects after approximately 11 days from the 1st prophylactic dose. To fit any logistical requirements, samples for PK analysis can be taken after prophylaxis dose #5-6, and whenever possible, sample collections should be during the longer partial interval of the alternating irregular dosing intervals. For example, if a subject follows a dosing regimen as follows:

Date	Weekday	Dose number	Interval	Time from 1st 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 profile will be assessed at the end of the study, i.e. 12* month ± 2 week visit with a PK 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 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). If the dosing interval for a certain switch subject wouldn't allow for the full 11 post-infusion timepoints sample collection, 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 for an individual switch subject.

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

* Study treatment period is extended by 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.

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

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, whether or not considered causally related to the IP.

12.1.1.1 Serious Adverse Event

An SAE is defined as an untoward medical occurrence that, at any dose, meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are (including but not limited to):
  - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
  - Reviewed and confirmed seroconversion for HIV, hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)

- Development of clinically significant neutralizing VWF antibodies
- Development of neutralizing antibodies to FVIII (titer ≥0.4 BU [by Nijmegen- modified Bethesda assay] or ≥0.6 BU [by Bethesda assay])
- Thromboembolic events (e.g., myocardial infarction, stroke, transient ischemic attack [TIA], deep vein thrombosis [DVT] or pulmonary embolism)
- Hypersensitivity reactions (e.g., anaphylaxis [for definition, refer to Section 12.6.2] and other immediate and delayed hypersensitivity reactions which may manifest with urticarial rash, pruritus, flushing, angioedema of the face, extremities, or laryngeal tissues [leading to throat tightness with stridor], wheezing, gastrointestinal symptoms, and/or hypotension)

Uncomplicated pregnancies, following maternal or paternal exposure to IP are not considered an AE/SAE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE and should be reported per SAE reporting guidelines provided in Section 12.1.2.3 (Safety Reporting).

12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any suspected adverse reaction to study treatment that is both serious and unexpected is considered a SUSAR.

The event(s) must meet all of the following:

- Suspected adverse reaction (which implies that there is reasonable evidence indicating a causal relationship between the event and the study treatment),
- Unexpected (per Reference Safety Information (RSI)/IB), and
- Serious

Once determined to meet the criteria for a SUSAR, the sponsor will ensure expedited SUSAR reporting is completed in line with the regulatory requirements in participating countries as outlined in the Safety Management Plan.

12.1.1.3 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet any of the seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) listed in section 12.1.1.1.

12.1.1.4 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (e.g., IB, PI [prescribing information]). "Unexpected" also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.1.1.5 Preexisting Disease

Preexisting diseases that are present before entry in to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described as "worsening" of the pre-existing condition on the AE CRF.

12.1.2 Assessment of Adverse Events

For the purposes of this study, the following will not be considered as AEs and will not be included in the analysis of AEs.

- Bleeding episodes are part of the underlying disease and therefore are not AEs; they will be evaluated in the context of efficacy.
  - For non-serious bleeding episodes caused by an injury, the injury would not be reported as an AE, unless it resulted in a medical finding other than a bleeding episode (e.g., abrasion of skin). Therefore, any VWD-related bleeding event (e.g., epistaxis, gastrointestinal bleeding, musculo-skeletal bleeding, menorrhagia) that is non-serious will not be reported as an AE. However, the investigator may decide that the event is an AE if the event also would have occurred in a healthy individual under the same circumstances.
  - For serious bleeding episodes (bleeding SAEs): Bleeding events that meet seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) should be captured on the SAE eCRF and reported as an SAE to the Sponsor or designee (e.g., CRO) on an SAE Report form as described in Section 12.1.2.3 (Safety Reporting).
- Seroconversion after documented HAV/HBV vaccination prior to or during the study period.

Each AE from the first IP exposure to the study completion date will be described on the AE CRF using the term representing medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial verbatim expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2

For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable, action taken with regards to the study treatment (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution or until the subject's condition returns to the level at the baseline for pre-existing conditions.

If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the protocol-specified dosage (including underdosing /overdosing [<20 IU/kg rVWF:RCo or >100 rVWF:RCo], abuse, and withdrawal, treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after administration of IP will be reported on a Pregnancy Form and followed-up at 1 year post-delivery, if feasible.

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the SAE Form within 24 hours after awareness: no additional reporting on CRFs is necessary.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, e.g., assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs

- Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP, is not biologically plausible per mechanism of action of the IP, or has a much more likely alternative etiology).

- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of IP
  - An alternative etiology is equally or less likely compared to the potential relationship to the IP
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
    - Reappearance of a similar reaction upon re-administration (positive re-challenge)
    - Positive results in a drug sensitivity test (skin test, etc.)
    - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
  - Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within 5 days after IP infusion, the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

12.1.2.3 Safety Reporting

AEs and SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Section 20.2) and Section 12.1.2.

Adverse Events and SAEs are to be recorded on the AE page of the eCRF. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the IP, must be reported immediately (within 24 hours of the study center's first knowledge of the event). All SAEs must be reported in English via the Electronic Data Capture (EDC) system by completing the relevant eCRF page(s) and also by SAE Report Form via fax/email to Sponsor's Global Drug Safety (Baxalta GDS) department within 24 hours of becoming aware of the event for SAEs (for contacts, instructions, and additional details, refer to the SAER form).

Within 24 hours of site awareness of a SAE (or Pregnancy) study sites will complete and send all SAE (or Pregnancy) reports to a dedicated:

Baxalta Global Drug Safety fax number: [redacted]

OR

email: [redacted]

The responsible Site Monitor will review the SAE (or Pregnancy) Reports for completeness, will reconcile the reports against the EDC database, and will follow-up with sites to obtain missing information and/or information requiring clarification. Any SAE associated with a pregnancy must be reported on the SAER Form.

For Follow-up Reports, the site shall use a new SAER form (marked as Follow-up) and the new information should be entered together with a brief narrative identifying the updated data.

An SAER should include the following minimum information:

1. Protocol Number (on all pages)
2. Subject identification number (on all pages) and demographics (gender, age at onset of event and/or date of birth)
3. Investigational product and treatment regimen (including date of the first dose of IP, date of the last dose of IP prior to the onset of the SAE)
4. Medical Term for Event (Diagnosis preferably)
5. Description of the SAE, including:
    - Date of onset
    - Causal relationship assessment by the Investigator
6. Seriousness criteria (e.g., death, life-threatening, hospitalization, medically significant, or other criterion)
7. Name, address, fax number, email, and telephone number of the reporter/Investigator

Post-trial SAE Reporting: In compliance to EudraLex Volume 10 (Clinical trials guidelines, Chapter II: Safety Reporting from the European Commission), which references an EMA guidance (ICH Topic E 2 A - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting), clinical sites/the investigator should report to the Sponsor SAEs after a subject´s study completion. Study sites will be provided a Post-Trial SAER form to complete and report these post-study SAEs to the Sponsor within the 24 hours of their awareness. Site Monitor will instruct the site that any such Post-Trial SAEs should be reported on the study-specific Post-Trial SAER form if/when the site becomes aware of it. Such information will not be actively monitored by the sponsor after completion of the study.

These events shall be reported to Baxalta GDS who will process them in the same way as SAEs occurring during the study. Post-Trial SAEs do not need to be captured in the study EDC database if it is already locked. Irrespective if captured in the EDC database or not, such Post-Trial SAEs will become part of the GDS database. The monitor should remind the clinical site about the post-trial SAE reporting requirements during interim monitoring visits, upon each subject's study completion as well as during the close-out visit.

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of the clinical trial
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor.
In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committees (ECs) and relevant competent authority(s) are notified of the urgent measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (i.e., from the time of signed informed consent up to but not including the first IP exposure) will be described on the SAER. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE.** NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g. reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (e.g., potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) 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. The subject's medical history will also include documented history of on-demand or pdVWF prophylaxis treatment for at least the past 12 months and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 months (up to 24 months if available).

All medications taken and non-drug therapies received in the 2 weeks prior to study entry and all concomitant medications and non-drug therapies during study will be recorded on the CRFs.

Data on medical history, drug and non-drug therapy history of those subjects who transition from surgery rVWF (vonicog alfa) study will be used from the eCRF of the main studies, will be updated, if applicable, and transcribed into the respective eCRF of the prophy study.

12.6 Physical Examinations

At screening and subsequent study visits (as described in Section 10.3), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 12.1.1.5), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.6.1 Thromboembolic Events

There is a risk of occurrence of thrombotic events, particularly in patients with known clinical or laboratory risk factors for thrombosis including low ADAMTS13 levels. Therefore, patients at risk must be monitored for early signs of thrombosis during the study and prophylaxis measures against thromboembolism should be instituted according to current recommendations and standard of care. Additional diagnostic procedures are required according to each institution's standard of care which may consist of, but are not limited to the following:

- For DVT: Magnetic Resonance Imaging (MRI), compression ultrasound or impedance plethysmography.
- For pulmonary embolism: ECG, chest radiography, perfusion/scintiscan or MRI.
- For myocardial infarction: ECG, cardiac enzymes, echocardiography
- For stroke: diffusion-weighted magnetic resonance imaging or computed tomography, ABCD scoring, carotid imaging

Results of diagnostic procedures may be forwarded to the sponsor to be reviewed by an independent external expert panel, such as the DMC, if applicable.

12.6.2 Anaphylaxis

The diagnosis of anaphylaxis is highly likely when any of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g, generalized urticaria, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
    b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a. Involvement of the skin or mucosal tissue (e.g., generalized urticaria, pruritus or flushing, swollen lips-tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c. Reduced BP or associated symptoms (hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to a known allergen for that patient (minutes to several hours):
    a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
    b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP

If a subject develops anaphylaxis in the course of the clinical study, this needs to be reported as SAE (Section 12.1.1.1). Additional blood will be drawn for Anti-VWF IgE antibody testing (Section 12.9.13).

12.7 Vital Signs

Vital signs will be assessed pre- and post-infusion at each visit, if not stated otherwise:

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

Vital signs (pulse rate, respiratory rate, and blood pressure) should be recorded within 30 min before and after IP administration. The assessment of vital signs per planned study visit is outlined in Supplement 20.2.

Vital sign values are to be recorded on the physical examination eCRF. For each vital sign value, the investigator will determine whether the value is considered an AE (see definition in Section 12.1). If assessed as an AE, the medical diagnosis (preferably), symptom, or sign, will be recorded on the AE eCRF. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE, should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.8 Electrocardiogram

A standard 12-lead ECG at rest will be performed at screening, at the 6 month follow-up visit and at the study termination visit and evaluated for medical significance by the investigator.

12.9 Clinical Laboratory Parameters

Refer to the Laboratory Manual for information on collection and processing of samples.

In general all laboratory tests will be performed at central laboratories, except the pregnancy and blood group test which will be performed at the local laboratory. In addition, relevant critical safety laboratory tests for complete blood count (CBC), serum chemistry and/or coagulation parameters such as VWF and FVIII activity may also be performed in the local laboratory to ensure that results will be available immediately to the investigator. In principle, results from the central laboratory will be used for data analysis purposes. The assays performed in the central laboratories are specified in the Laboratory Manual. The investigator will supply the sponsor with a list of the normal ranges and units of measurement for the laboratory variables to be determined at the site. Laboratory values such as antibodies to other proteins are not required immediately and will be assessed later during the course of the study.

Any abnormal laboratory value that is considered clinically significant by the investigator based on a local laboratory test result (reference range and the units to be provided) should be confirmed by a central laboratory test result for which the sample is drawn/collected within 24 hours of the abnormal finding by the local laboratory.

12.9.1 rVWF Pharmacokinetics and Pharmacodynamics

Details on pharmacokinetic and pharmacodynamics assessments are provided in Section 11.6.

12.9.2 Hematology and Clinical Chemistry

The hematology panel will consist of CBC [hemoglobin, hematocrit, erythrocytes (ie, red blood cell count [RBC]; mean corpuscular volume [MCV], mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration [MCHC]), and leukocytes (i.e., white blood cell count [WBC])] with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.

The clinical chemistry panel will consist of sodium (Na), potassium (K), chloride (Cl), ALT, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase (AP), blood urea nitrogen (BUN), CR, and glucose (Glu).

Blood will be obtained for assessment of hematology and clinical chemistry parameters at screening, during PK-assessment prior to rVWF (vonicog alfa) IP infusion, after 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours post rVWF (vonicog alfa) IP infusion, at all follow-up visits as per schedule (refer to Supplement 20.3 Clinical Laboratory

Assessments), i.e., 4 weeks ± 1 week, 8 weeks ± 1 week and every 3 months ± 2 weeks, and at study completion. Hematology and clinical chemistry assessments will be performed on Ethylenediaminetetraacetic acid (EDTA)-anticoagulated whole blood and serum, respectively, at the central laboratory.

12.9.3 Immunology

12.9.3.1 Antibodies to VWF and FVIII

All subjects will be tested for binding and neutralizing antibodies to VWF and FVIII at screening, at initial PK assessment, at each of the scheduled follow-up visits and at the study completion visit. Testing will be done prior to IP infusion and with at least a 72 hour wash out period since the last IP infusion. If there is any suspicion of inhibitor development (e.g. excessive bleeding) binding and neutralizing antibodies to VWF and FVIII may be tested at the discretion of the investigator.

12.9.3.2 Neutralizing and Total Binding Anti-VWF Antibodies

The assays to establish the presence of neutralizing and total binding anti-VWF antibodies have been established in the absence of international standards and with only limited numbers of positive controls. Therefore, caution is advised in interpreting positive results. In particular, any clinical association, changes in the natural history of the disease, effect of therapy, etc. needs to be taken into account for final judgment. The sponsor's Medical Director should be consulted for additional advice. As part of the AE follow-up, any sample testing positive needs to be confirmed after 2-4 weeks for central laboratory testing. Only confirmed neutralizing anti -VWF antibodies are considered inhibitors (see Section 12.9.3.4). These subjects need to be closely monitored and therapy adjusted accordingly.

12.9.3.3 Binding antibodies to VWF

The presence of total binding anti-VWF antibodies will be determined by an enzyme-linked immunosorbent assay (ELISA) employing polyclonal anti-human Immunoglobulin (Ig) antibodies (IgG, IgM and IgA). For this assay (ELISA), recombinant human VWF will be coated onto a microtiter plate, then incubated with dilutions of the positive control, the negative control or test sample. Antibodies against human VWF that are present in the samples bind to the coated antigen and will be detected with a horseradish peroxidase (HRP)-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a human monoclonal antibody specific for human VWF spiked into the negative control. The negative control for this assay is pooled normal human plasma.

Plasma samples are analyzed for binding antibodies against the specific antigen in two steps. First, the sample is screened for antibodies and the titer of binding antibodies is determined. Second, the specificity of positive antibody results is confirmed.[16]
In brief, all samples are serially diluted (initial dilution 1:20 and further diluted 1:2).

The titer endpoint, defined as the highest dilution that still gives a positive signal above cut off level, is determined in two independent duplicates. The cut off level is established based on background signal level of healthy plasma donors (n=160) and set to include 5% false positives to be as sensitive as possible (95% percentile). The ELISA assay is validated allowing an assay variability of ± 1 titer step. Therefore, differences ≤ 2 titers steps may be due to variability of the ELISA assay. Specificity has to be confirmed in a competition assay when a sample has a titer of 1:80 or higher in the screening assay. Based on the validation criteria samples tested in the screening assay at 1:20 or 1:40 cannot be confirmed in the competition assay. A positive screening value is confirmed if the difference between the titers determined for the subject sample (re-screen) and for the subject sample with pre-incubation (confirmation sample) is > 2 titer steps. Antibody titers of subject samples will only be reported as positive, if the results of the screening and confirmatory analysis fulfill these acceptance criteria. The titer to be reported is always the one determined in the original screening procedure (independent of the result of the re-screening in the confirmation procedure).

A more detailed test procedure will be supplied upon request or pro-actively if a sample tests positive. A treatment related increase of the binding anti-VWF antibodies is expected, if the titer increases by more than 2 titration steps. These subjects need to be closely monitored and therapy adjusted accordingly.

12.9.3.4 Neutralizing Antibodies to VWF

Three functional VWF assays, VWF:CB, VWF:RCo and VWF:FVIIIB assays, will be used to test for the presence of neutralizing anti-VWF antibodies. Neutralizing antibodies to VWF:RCo, VWF:CB and VWF:FVIIIB activities will be measured by assays based on the Bethesda assay established for quantitative analysis of FVIII inhibitors (Nijmegen modification of the Bethesda assay).[17] The amount of inhibitor is expressed as BU per mL. One BU is thereby defined as the amount of inhibitor that decreases the measured activity in the assays to 50% of that of the negative control samples. The assays were validated using human plasma samples from two type 3 VWD patients with low (1-2 BU/mL) and high (~10 BU/mL) titer inhibitors and plasma samples from non-human primates immunized with human rVWF (vonicog alfa) (>100 BU/mL).

If a subject has a measurable baseline level of VWF activity in the respective assay, it is taken into account in the calculation of the residual activity. However, if baseline levels are too high (>15% VWF:RCo), inhibitors may not be reliably detected.

To exclude false positive results, the detection limit for anti-VWF inhibitors was set to 1 BU/ml for all 3 assays. The rationale for this cut-off value is the relatively high CI of the underlying assays, making determinations at the end of the evaluation range of the Bethesda reference curve uncertain.[18] A more detailed test procedure may be requested to further characterize the anti-VWF inhibitors, if detected.

Only confirmed positive anti-VWF inhibitor test result will be reported and will be considered as a medically significant SAE.

12.9.3.5 Binding Antibodies to FVIII

Binding antibodies against FVIII will be analyzed using a proprietary enzyme immunoassay. The testing strategy will be as described for binding anti-VWF antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.3.6 Neutralizing Antibodies (Inhibitors) to FVIII

Neutralizing antibodies (inhibitors) to FVIII will be assessed by the Nijmegen modification of the Bethesda assay in a central laboratory. To verify a FVIII inhibitor, additional testing (such as tests for Lupus anticoagulants) may be initiated. Positive FVIII inhibitor tests will be defined as $\geq$ 0.4 BU by the Nijmegen-modified Bethesda assay that is confirmed by a second test performed on an independent sample obtained 2-4 weeks following the first test. Only confirmed positive FVIII inhibitor test result will be reported.

12.9.4 Antibodies to Other Proteins

Plasma will be assayed for the presence of antibodies against CHO protein (total Ig), murine IgG and human Furin (total Ig) using proprietary enzyme immunoassays. The testing strategy will be as described for binding anti- VWF antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.4.1 Anti-CHO Protein

Total Ig antibodies (IgG, IgA, IgM) against CHO protein will be analyzed. For this assay (ELISA), CHO protein derived from cultures of untransfected cells and propagated under the identical cell culture conditions used for ADVATE (rFVIII, octocog alfa) production will be coated onto a microtiter plate, then incubated with dilutions of the positive control, negative control or test sample. Antibodies against CHO protein that are present in the samples bind to the coated antigen and will be detected with a HRP-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a polyclonal goat anti-CHO protein antibody spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.4.2 Anti-Murine IgG

A commercially available ELISA (Medac, Hamburg, Germany) will be used to detect and to quantify IgG antibodies originating from human plasma that are directed against mouse-IgG (HAMA: human anti- mouse antibodies). Microtiter plates coated with mouse IgG will be incubated with dilutions of the standard, the positive control, the negative control or the test sample. Antibodies against mouse IgG that are present in the samples bind to the coated antigen and form a bridge to a peroxidase coupled mouse IgG antibody that will be used for detection (bridging format of the ELISA assay). The positive control for this assay will be a polyclonal goat anti-murine IgG spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.4.3 Antibodies to Human Furin

Total Ig antibodies (IgG, IgA, IgM) against human Furin will be analyzed. For this assay (ELISA), recombinant human Furin will be coated onto a microtiter plate, then incubated with dilutions of the positive control, the negative control or test sample. Antibodies against human Furin that are present in the samples bind to the coated antigen and will be detected with a HRP-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a human monoclonal antibody specific for human Furin spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.5 Viral Serology

The following viral seromarkers will be assessed at screening:

- HIV: anti-HIV 1, HIV 2
- HAV: anti-HAV (IgG and immunoglobulin M [IgM])
- HBV: Hepatitis B surface antigen (HbsAg), anti-Hepatitis B (HB) core, anti-HBs

- HCV: anti-HCV ELISA
- Parvovirus B19: anti-B19V (IgG and IgM)

Virus serology will be established during the screening period. The relevant confirmatory Polymerase Chain Reaction (PCR) testing may be performed from appropriate left-over samples as needed.

12.9.6 Urinalysis (Dipstick)

The urinalysis will include assessments for erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite and pH and will be performed at the central laboratory.

12.9.7 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. The pregnancy test may need to be repeated during the course of study in countries where mandated by national law.

12.9.8 VWD Mutational Analysis, Multimer Analysis and Human Leukocyte Antigen Genotyping

A cell pellet (buffy coat and erythrocytes) will be retained at the screening visit for VWD gene mutational analysis, VWF multimer analysis and HLA genotype determination if the information is not already available in the subject's medical history. Results from multimer analysis (see Section 12.9.10.1) may contribute to VWD gene mutational analysis. The genetic testing will be done, when the subject consents to the genetic testing.

12.9.9 Blood Group Analysis

The blood group needs to be determined during the screening period. If the information is not already available in the subject's medical history, it has to be determined at the local lab.

12.9.10 Additional Laboratory Testing in Case of Thromboembolic Events

rVWF (vonicog alfa) contains ULMW multimers because of a lack of exposure to endogenous VWF protease (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) during the manufacturing process. In vitro and in vivo cleavage of these ultralarge molecular fractions by ADAMTS13 and generation of characteristic satellite bands has been extensively demonstrated during nonclinical and clinical development. Nevertheless, the potential elevated risk of thrombosis and/or other thromboembolic complications due to the administration of ultra large molecular VWF multimers in subjects with normal levels of VWF cannot be completely excluded. Therefore VWF multimer analysis will not only be performed routinely at screening but in case of thromboembolic events, both VWF multimer analysis as well as ADAMTS13 activity will be determined to assess any relatedness of these occurrences with IP treatment.

12.9.10.1 VWF Multimer Analysis

The VWF multimer pattern will be assessed using low-resolution sodium dodecyl sulfate (SDS)–agarose gel electrophoresis. High-resolution SDS–agarose gel electrophoresis, with agarose concentrations >1.5%, will be used to determine the satellite band structure of VWF. These analyses will employ Western blot with luminescence video imaging.

12.9.10.2 ADAMTS13 Activity

VWF73 was identified as the 73 amino acid minimal region of the VWF A2 domain required for ADAMTS13 cleavage. The cleavage of this substrate will be detected by a commercially available ELISA-based Chromogenic assay (Technoclone Austria): Cleavage of immobilized VWF73 substrate is detected by a HRP-labeled antibody directed against the cleavage site of VWF73. The amount of bound antibody, which is the function of the ADAMTS13 cleavage is detected by a chromogenic substrate.

12.9.11 Soluble P-Selectin (sP-Selectin)

sP-selectin is a cell adhesion molecule (CAM) found in granules in endothelial cells (cells lining blood vessels) and activated platelets. Data for an association between the sP-selectin concentration, TTP and venous thromboembolism (VTE) are limited and the predictive value has not yet established. A commercial ELISA assay will be employed as an exploratory test. sP-selectin will be determined at the Screening visit and used as indicator for an increased thrombotic risk.

12.9.12 D-Dimer

D-dimer will be used as a marker for DVT and disseminated intravascular coagulation (DIC). While a negative result practically rules out thrombosis, a positive result can indicate thrombosis but does not rule out other potential etiologies, including a recent hemorrhage. Its main use, therefore, is to exclude thromboembolic disease where the probability is low. D-Dimer will be measured at the Screening visit and used as indicator for an increased thrombotic risk.

12.9.13 Additional Laboratory Testing in Case of Severe Hypersensitivity Reactions

If a subject develops a severe hypersensitivity reaction in the course of the clinical study, additional blood will be drawn for anti-VWF IgE antibody testing. The presence of anti-VWF IgE will be determined by using the ImmunoCAP®, a VWF-specific IgE blood test (Thermo Scientific). The basis of the ImmunoCAP® technology is a cellulose polymer as solid phase in a plastic capsule providing a large surface for protein binding. rVWF (vonicog alfa) as antigen is covalently coupled to the cellulose polymer.

Detection of specific anti-VWF IgE bound to the antigen will be accomplished by a secondary enzyme-labeled anti-human IgE antibody. Testing for binding anti-human VWF IgE antibodies will be done with 0.5 mL plasma. Antibody containing samples will be identified and quantified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.14 Assessment of Laboratory Values

12.9.14.1 Assessment of Abnormal Laboratory Values

For VWF and FVIII laboratory assessments no evaluation of clinical significance is necessary.

Each other laboratory value (except results to determine genetics of the underlying VWD disease and blood group) has to be assessed by the investigator and the assessment will be recorded on the eCRF. The investigator will determine for each abnormal laboratory value whether the value is considered clinically significant or not and provide the reference range including the units. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 12.1) and record the sign, symptom, or medical diagnosis on the AE CRF, is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.5), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, i.e. because it is due to a preexisting disease, due to a lab error, due to variation or due to another issue that will be specified.

Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator. Any abnormal laboratory value that is considered clinically significant by the investigator based on a local laboratory test result (reference range and the units to be provided) should be confirmed by a central laboratory test result for which the sample is drawn/collected within 24 hours of the abnormal finding by the local laboratory.

Any seroconversion result for HIV, HAV, hepatitis B virus (HBV), HCV, HEV, or B19V shall be re-tested.

12.10 [redacted]

12.10.1 [redacted]

12.10.2 [redacted]

[redacted]

13. STATISTICS

13.1 Sample Size and Power Calculations

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 cohort (OD and switch). A total of at least 5 type 3 VWD subjects will be followed for 12 months. 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).[1]

13.2 Datasets and Analysis Cohorts

13.2.1 Safety Analysis Set

The Safety Analysis Set will be composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

13.2.2 Full Analysis Dataset

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

13.2.3 Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set will be composed of subjects who are at least 70% compliant regarding the number of scheduled prophylactic infusions (as measured by the ratio of actual number of infusions to planned number of infusions). Only subjects who met all study entry criteria and who had no major protocol violations that might impact primary efficacy assessments will be included in the PP analysis set.

13.2.4 PK Full Analysis Set

The Pharmacokinetic Full Analysis Set (PKFAS) will be composed of all subjects who received the PK infusion and who provided acceptable data for PK and PD analysis. Acceptable PK/PD data will be defined in the Statistical Analysis Plan.

13.2.5 PK Per Protocol Analysis Set

The Pharmacokinetic 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 affecting the PK period of the study as defined in the detailed Statistical Analysis Plan.

13.3 Handling of Missing, Unused, and Spurious Data

13.3.1 General

Statistical techniques will not be used to identify and exclude any observations as outliers from the analyses. If data are considered spurious, e.g. for lack of biological plausibility, it will be documented to include the reason for exclusion and the analyses from which the data were excluded.

13.3.2 Other

1. Regarding missing data in PK records:
    - Body weight: If a subject's weight is missing from the PK infusion record, the subject's last recorded weight will be used to calculate the weight-adjusted dose.
    - Concentration:
        - Baseline concentration levels reported as below the limit of quantification will be considered to be 0. Missing VWF baseline concentration levels (VWF: RCo, VWF: AG or VWF: CB) for Type 3 subjects will be set to 0.
    - Time:
        - If start time of infusion is missing (but stop time is available) and actual collection time is available, then stop time of infusion will be taken for further calculation (i.e. time difference between actual end date/time of infusion and date/time blood sample drawn).
        - If actual collection date/time is missing and planned collection date/time is missing, then this PK time point will be taken out from the PK analysis (i.e. no data entry for this time point).
        - For all other scenarios, the planned collection date/time will be taken for further calculation.
2. Regarding missing data in AE records:
    - Handling of unknown causality assessment:
        - If a subject experiences an AE with a missing causality assessment, the relationship of the AE will be counted as "related."

- Handling of unknown severity grades:
  - If a subject experiences more than one AE categorized under the same preferred term, 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.

13.4 Methods of Analysis

The study success criteria are the objectives as stated in Section 7. “Treatment success” was defined as the extent of control of bleeding episodes achieved during this study.

13.4.1 Primary Outcome Measure

The primary outcome measure is ABR for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa). No formal statistical hypothesis test is planned for the analysis. The primary efficacy analysis will be based on the FAS and will be summarized by the two cohorts: on-demand and switch subjects. As a supportive analysis, the same analysis will also be carried out on the PP analysis set.

The spontaneous ABR while treated with rVWF (vonicog alfa) for each cohort will be estimated using a negative binomial regression. The prior ABR will be based on historical data collected from each enrolled subject.

The two ABRs (prior to prophylaxis treatment and while on prophylaxis) for each cohort will be compared within each subject using a generalized linear mixed-effects model (GLMM) (with a logarithmic link function, the default for the negative binomial distribution), accounting for the fixed effect of the two treatments. The follow-up time (in years) will be specified as an offset. The ratio of ABR while in the study to historical ABR will be estimated and reported together with the 95% confidence interval for each of the two cohorts.

The difference in on-study ABR relative to historical ABR will be also summarized descriptively.

13.4.2 Secondary Outcome Measures

In general, data for secondary efficacy analysis will be summarized by the two cohorts: on-demand and switch subjects and when applicable overall. Mean, standard deviation, median, range, quartiles will be calculated for continuous endpoints. Proportions, will be calculated for categorical endpoints. Confidence intervals at the two-sided 95% level will be provided when appropriate.

13.4.2.1 Additional Efficacy of Prophylaxis Treatment with rVWF

The number and proportion of on-demand subjects with ABR percent reduction success (i.e.≥ 25%) will be calculated together with a two-sided, 95% CI for the proportion.

The number and proportion of pdVWF switch subjects ABR preservation success will be reported together with the corresponding 95% two-sided CIs for the proportion.

The number and proportion of subjects with categorized spontaneous ABR (i.e. 0, 1-2, 3-5, more than 5 bleeds) will be reported descriptively.

Summary statistics for the total number of infusions, as well as average number of infusions per week will be provided. The total weight adjusted consumption of rVWF (vonicog alfa) during prophylactic treatment will be provided. If applicable, historical data on consumption of pdVWF prior to the study will be summarized as well.

The change in spontaneous ABR from the historical rate to that during the rVWF (vonicog alfa) prophylaxis period will be summarized by location of bleeding (GI, epistaxis, joint bleeding, menorrhagia, oral and other mucosa, muscle and soft tissue, etc.).

13.4.2.2 Pharmacokinetic and Pharmacodynamic Analysis

All PK and PD analyses will use the actual sampling times, not nominal times specified in the protocol, wherever possible. Actual sampling times will be defined as time from the start of infusion to the blood sample collection time. A deviation from the protocol-specified blood sample 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 results were biologically implausible will be eliminated from the analysis.

If any concentration data are considered spurious (e.g. lack of biological plausibility), the reason for exclusion from the analysis and the analysis from which the data point was excluded will be documented.

Details of calculation of PK and PD parameters and corresponding analysis will be given in the statistical analysis plan.

The following PK parameters, based on the initial PK assessment after a washout for on-demand subjects, will be listed and summarized descriptively for VWF:RCo, VWF:Ag and VWF:CB: IR, $T_{1/2}$, MRT, $AUC_{0-\infty}$, $AUC_{0-tlast}$, C_{max}, T_{max}, V_{ss}, and CL. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity, based on the initial PK assessment after a washout for on-demand subjects will be assessed using C_{max}, T_{max}, and $AUC_{0-tlast}$. These PD parameters will be listed and summarized descriptively. PK parameters at steady state ($AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$) for the partial dosing interval will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study for VWF:RCo, VWF:Ag and VWF:CB and summarized descriptively for subjects with the same dosing regimens. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity will be assessed using $AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$. These PD parameters will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study and will be summarized descriptively for subjects with the same dosing regimens.

For the on-demand subjects, the PK of VWF:RCo will be analyzed using a population PK approach to characterize the single and multiple dose pharmacokinetics, including associated variability assessed at after washout and at end of study, respectively. The population PK analysis will be performed in a stepwise manner as outlined below.

1. Exploratory graphical analysis of VWF:RCo versus time data for identification of potential outliers and to inform the pharmacometric analysis.
2. Population PK model development for rVWF (vonicog alfa):
    a. Evaluate alternative structural and stochastic models to describe the typical and individual rVWF (vonicog alfa) profiles.
    b. Investigate and characterize the potential for a time dependency in CL of rVWF (vonicog alfa).
    c. Evaluate, and if necessary refine, the candidate final model

Details of this Population PK analysis will be given in a separate Population PK analysis plan.

For the switch subjects, differences in $AUC_{0\text{-}tau;ss}$, $C_{max;ss}$, and $C_{min;ss}$ assessess shortly after reaching steady state and assessed at the end of the study will be assessed by the ratio of geometric means and corresponding two-sided 95% confidence intervals for VWF:RCo, VWF:Ag,VWF:CB, and FVIII:C. These analyses will be performed using a linear mixed effects model with PK assessment (i.e. factor of two levels relating to the PK assessment shortly after reaching steady state and the PK assessment at end of study, respectively) as a fixed effect and subject as a random effect based on log-transformed PK parameters. 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.

Descriptive statistics will be used to summarize VWF:RCo, VWF:AG and VWF:CB and FVIII:C levels for each nominal time point on the PK curve.

For all subjects in the PKFAS activity/concentration vs. time curves will be prepared.

Formulas for PK parameters IR, $T_{1/2}$, MRT, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}tlast}$, C_{max}, T_{max}, V_{ss}, and CL, $AUC_{0\text{-}tau;ss}$, $C_{max;ss}$, $T_{max;ss}$,and $C_{min;ss}$ will be given in the statistical analysis plan and will be derived using non-compartmental methods in WinNonlin. Analysis of these parameters will be carried out on the PKFAS as well as on the PKPPAS.

13.4.2.3 Safety

Safety analysis will be performed overall and by the two cohorts: on-demand and switch subjects.

TEAEs are defined as AEs with start dates on or after the first exposure to IP. Summaries of AEs will be based on TEAEs unless otherwise indicated.

Occurrence of AEs and SAEs will be summarized descriptively, by system organ class and preferred term. The number and percentage of subjects who experienced AEs and SAEs, and the number of AEs and SAEs will be tabulated. In addition, the number of subjects who experienced AEs assessed as related to IP by the investigator, and the number of IP-related AEs will be tabulated. The number of patients with AEs by severity will be presented similarly.

A listing of all AEs will be presented by subject identifier, age, sex, preferred term and 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.

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 infusion, irrespective of being related or not related to treatment. Temporally associated AEs will be presented in summary tables.

AEs that occurred before first IP infusion will be listed separately.

Adverse events of special interest (AESI), such as hypersensitivity reactions and thromboembolic events, will be monitored throughout the study and statistical analysis will be conducted based on the search criteria (eg, standardised MedDRA queries [SMQ]) determined prior to database lock, and summarized.

For immunogenicity, frequency counts and percentages will be calculated for 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. Clinically significant changes relative to baseline in vital signs and clinical laboratory parameters (hematology, clinical chemistry) will be reported.

13.4.3 Exploratory Outcome Measures

[redacted]

13.4.3.1 [redacted]

[redacted]

13.4.3.2 [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

13.4.3.3 [redacted]

[redacted]

13.4.3.4 [redacted]

[redacted]

13.5 Planned Interim Analysis of the Study

No formal interim analysis is planned for this study.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Trial Agreement (CTA). If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the CTA.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable national and local regulatory requirements as described in the CTA. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

15.1.1 Investigator Report and Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the CTA. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the CTA. Auditing processes specific to the study will be described in the audit plan.

15.5 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. Also, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing whenever pdVWF is used instead of rVWF (vonicog alfa). The reason for this use must also be provided to the sponsor.The sponsor (Baxalta) will also ensure the responsible EC and relevant competent authority are notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.6 Laboratory and Reader Standardization

A central laboratory/reader will be used for all clinical assessments except for pregnancy testing and blood group test (refer to Section 12.9). Local laboratories are requested to provide their laboratory specifications of the individual tests that are also being tested locally.

16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the CTA.

16.2 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the CTA.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

16.3 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients and/or their legally authorized representative must sign an informed consent form before entering into the study according to applicable national and local regulatory requirements and ICH GCP. Before use, the informed consent form will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 16.2). The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable national and local regulatory requirements. Patients or their legally-authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent form, patients or their legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised informed consent form, which have been approved by the applicable EC and regulatory authorities, will be provided by the investigator to the subjects who consented to participate in the study

16.4 Data Monitoring Committee

This study will be monitored by a DMC. The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. 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 stop a trial if it finds toxicities or if treatment is proven to be not beneficial. Details will be defined in the DMC charter.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the CTA.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.7), records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, CRFs, SAERs, laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

If electronic format CRFs are provided by the sponsor, only authorized study site personnel will record or change data on the CRFs. If data is not entered on the CRFs during the study visit the data will be recorded on paper and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (e.g., ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the CTA.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the CTA.

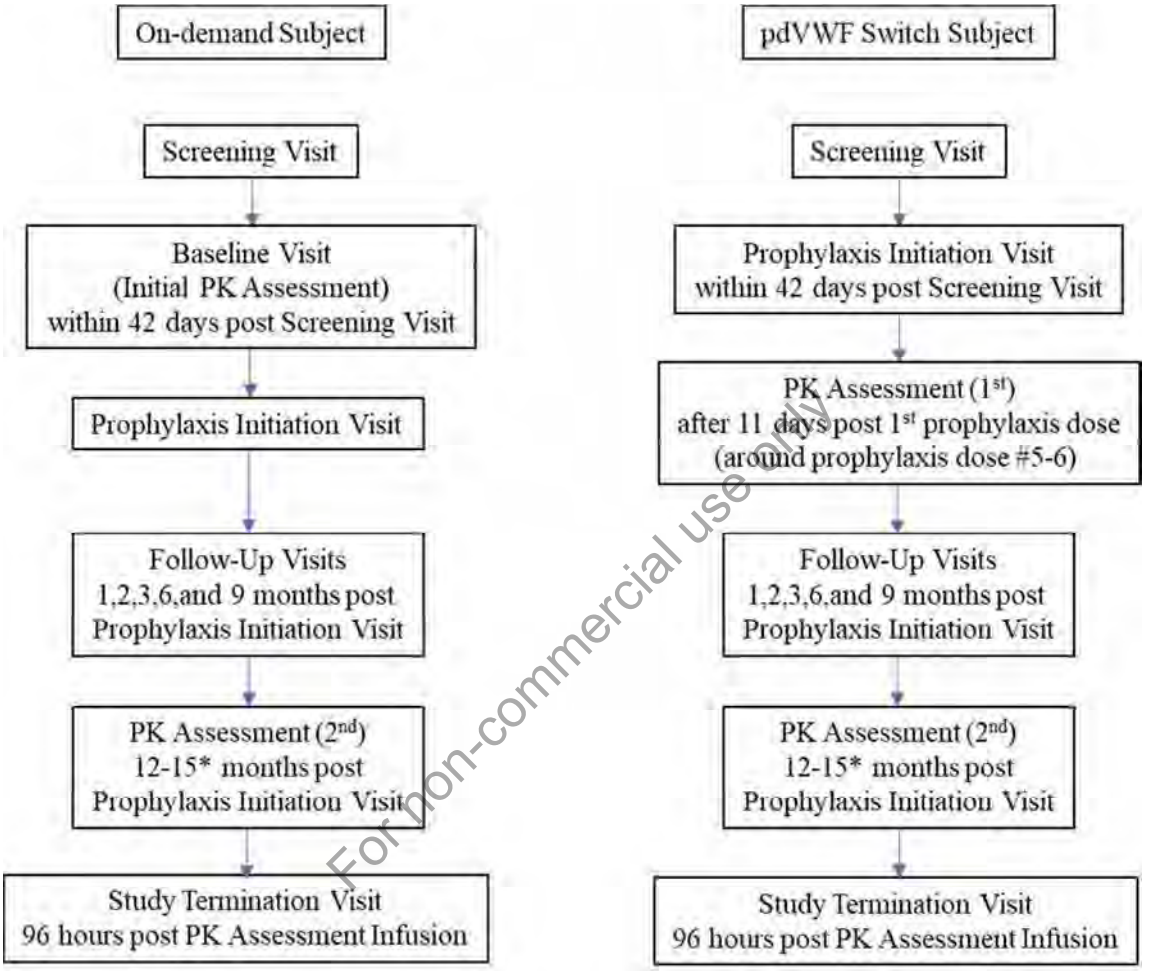
19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the CTA.

20. SUPPLEMENTS

20.1 Study Flow Chart

Figure 1
Study Design for Baxalta Clinical Study 071301



* Study treatment period is extended by 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.

20.2 Schedule of Study Procedures and Assessments

Table 6a
Schedule of Study Procedures and Assessments for On-demand Subject

Procedures/ Assessments	Screening Visit	Baseline Visit (PK-assessment visit)			Prophylaxis Initiation Visit	Interval/Follow-Up Study Visits					PK Assessment at Study Completion			Termination Visit
		Pre-infusion[g]	Infusion	Post-infusion[g]		1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion[g]	Infusion	Post-infusion[g]	Conducted at the 96 hour postinfusion PK Assessment
											12-15[i] month ± 2 weeks			
Informed Consent [a]	X													
Eligibility Criteria	X													
Medical History[b]	X													
Concomitant Medications[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-drug Therapies[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X			X	X	X	X	X	X	X			X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Bleeding Episodes and Treatment and Hemostatic Efficacy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratories	X	X		X	X[h]	X	X	X	X	X	X		X	X
Vital Signs[d]	X	X		X	X	X	X	X	X	X	X		X	X
ECG	X								X					X
IP Treatment[e]			X		X	X	X	X	X	X		X		
IP Consumption / Treatment Compliance						X	X	X	X	X				
Subject Diary					X	X	X	X	X	X				
[redacted]	X[f]								X					X

Continued on next page

Continued

[a]) Occurs at enrollment (before screening).
[b]) Including documented history of on-demand treatment for the past 12 months (up to 24 months if available) and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 (up to 24) months.
[c]) Including all medications and non- drug therapies taken in the 2 weeks prior to study entry and all the concomitant medications and non-drug therapies during the course of the study.
[d]) Vital signs: height, weight, body temperature, pulse rate, respiratory rate, and blood pressure. Height is only required at the screening visit. The time points for pre- and post-infusion measurements are (weight is measured pre-infusion only): within 30 minutes before infusion start and 30 ± 15 minutes post-infusion.
[e]) IP treatment after the prophylactic treatment initiation visit at the site will be continued as home-treatment if the subject qualifies; a wash-out period of at least 72 hours is required after the last IP infusion before the follow-up visit. IP infusion will be given at the study site after the blood sample for immunology testing and IR determination is drawn.
[f]) Can be done either at the screening or the baseline visit.
[g]) Time points for PK blood draws: 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 (the 96 hr sampling can be omitted if not allowed by the dosing interval).
[h]) If a subject did not undergo PK assessment, laboratory assessments will be performed at this visit.
[i]) Study treatment period is extended by 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. In this case, 12 month ± 2 weeks visit is to be considered as a follow-up visit, and EOS visit is to be performed once the subject can rollover into the continuation study, from 12 month ± 2 weeks to 15 month ± 2 weeks post prophylaxis initiation visit, as applicable.

Table 6b
Schedule of Study Procedures and Assessments for pdVWF Switch Subject

Procedures/ Assessments	Screening Visit	Prophylaxis Initiation Visit	PK Assessment (at prophylaxis dose #5-6)			Interval/Follow-Up Study Visits					PK Assessment at Study Completion			Termination Visit
			Pre-infusion[g]	Infusion	Post-infusion[g]	1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion[g]	Infusion	Post-infusion[g]	Conducted at the 96 hour postinfusion PK Assessment
											12-15[h] month ± 2 weeks			
Informed Consent [a]	X													
Eligibility Criteria	X													
Medical History[b]	X													
Concomitant Medications[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-drug Therapies[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X	X			X	X	X	X	X	X			X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Bleeding Episodes and Treatment and Hemostatic Efficacy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratories	X	X	X		X	X	X	X	X	X	X		X	X
Vital Signs[d]	X	X	X		X	X	X	X	X	X	X		X	X
ECG	X								X					X
IP Treatment[e]		X		X		X	X	X	X	X		X		
IP Consumption / Treatment Compliance						X	X	X	X	X				
Subject Diary		X				X	X	X	X	X				
[redacted]	X[f]								X					X

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Continued

[a]) Occurs at enrollment (before screening).
[b]) Including documented history of prophylaxis treatment for the past 12 months (up to 24 months if available) and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 (up to 24) months.
[c]) Including all medications and non- drug therapies taken in the 2 weeks prior to study entry and all the concomitant medications and non-drug therapies during the course of the study.
[d]) Vital signs: height, weight, body temperature, pulse rate, respiratory rate, and blood pressure. Height is only required at the screening visit. The time points for pre- and post-infusion measurements are (weight is measured pre-infusion only): within 30 minutes before infusion start and 30 ± 15 minutes post-infusion.
[e]) IP treatment after the prophylactic treatment initiation visit at the site will be continued as home-treatment if the subject qualifies; a wash-out period of at least 72 hours is required after the last IP infusion before the follow-up visit. IP infusion will be given at the study site after the blood sample for immunology testing and IR determination is drawn.
[f]) Can be done either at the screening or the prophylaxis initiation visit.
[g]) Time points for PK blood draws: 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 (the 96 hr sampling can be omitted if not allowed by the dosing interval).
[h]) Study treatment period is extended by 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. In this case, 12 month ± 2 weeks visit is to be considered as a follow-up visit, and EOS visit is to be performed once the subject can rollover into the continuation study, from 12 month ± 2 weeks to 15 month ± 2 weeks post prophylaxis initiation visit, as applicable.

20.2.1 Summary Schedule of Visit Assesments for Surgical Bleeding

Table 7
Summary Schedule of Visit Assesments for Surgical Bleeding

Procedures/ Assessments	**Surgical procedure**				**Post-Operative Day 7 Visit (± 1 day)**	**Post-Operative Day 14 Visit (± 2 day)**
	Priming Dose Procedures (12-24 hours prior to surgery)	**Loading Dose Procedures (≤ 3 hours prior to surgery)**	**Intraoperative**	**Postoperative (day 1 → end of perioperative IP treatment)[a]**		
ECG						X
Physical examination[b]	X	X		X	X	X
Adverse events	X	X	X	X	X	X
Laboratories[c]	X	X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X
IP treatment: rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) or rVWF (vonicog alfa) only infusion	X	X as required	X as required	X as required	X as required	X as required
Concomitant medications and non-drug therapy	X	X	X	X	X	X
[redacted]						X
Hemostatic efficacy assessments[e]			X	X	X	X
Blood loss		X estimated	X actual	X	X[f]	X[f]
Treatment days estimate		X				

Continued on next page

Continued

[a)] The assessments will be performed daily until perioperative IP treatment end (potentially multi-visits)
[b)] Physical Examination: within 2 hours prior to IP infusion start
[c)] For laboratory assessments, see Table 9
[d)] Vital signs: within 30 minutes before infusion start and 30 ± 15 minutes post-infusion
[e)] Completed immediately postsurgery by the operating surgeon 24 hours post last IP infusion or at Day 14 visit (whichever occurs first) by the investigator
[f)] In case bleeding still ongoing

20.3 Clinical Laboratory Assessments

Table 8a
Clinical Laboratory Assessments for On-demand Subject

Procedures/ Assessments	Screening Visit	Baseline Visit (PK-assessment visit)			Prophylaxis Initiation Visit[k]	Interval/Follow-Up Study Visits					PK Assessment[m] at Study Completion			Termination Visit
		Pre-infusion	Infusion	Post-infusion		1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion	Infusion	Post-infusion	Conducted at the 96 hour postinfusion PK Assessment
											12-15[n] month± 2 weeks			
Hematology [a]	X	X		X	X	X	X	X	X	X	X		X	X
Clinical Chemistry[b]	X	X		X	X	X	X	X	X	X	X		X	X
Coagulation Panel/ PK assessment[c]	X	X		X	X	X	X	X	X	X	X		X	
Immunogenicity[d]	X	X			X[l]	X	X	X	X	X	X			X
Viral Serology[e]	X													
Urinalysis[f]	X													
VWD Gene Mutational Analysis / HLA genotype analysis and Analysis of VWF multimers[g]	X													
sP-selectin and D-dimer	X[h]													
Blood Group[i]	X													
Pregnancy Test[j]	X													

[a)] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. Hematology assessments during PK assessments will be determined prior to IP infusion and 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours thereafter. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

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[b)] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin. Clinical chemistry will be determined prior to IP infusion and after 24 ± 2 h, 48 ± 2 hours and 72 ± 2 hours during the PK assessments. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

[c)] Coagulation panel/PK assessment (also refers to IR pre/post dose assessments at prophy initiation visit and each follow-up visit): PT, INR and aPTT (only for screening), VWF:RCo, VWF:Ag, VWF:CB, FVIII:C,; during the PK assessment at the baseline visit blood samples will be drawn 30 min prior PK infusion; once the PK infusion is completed 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 and VWF:RCo, VWF:CB, VWF:Ag, FVIII:C will be determined; for follow-up visits, IR samples will be drawn within 30 minutes pre-infusion and 30 ± 5 minutes post-infusion. During screening and in case of thromboembolic event VWF multimers and ADAMTS13 will be analyzed to judge on a possibly relatedness to UHMW fractions of the IP.

[d)] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII –Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG . In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined. For on-demand subjects, a washout period of at least 72 hours after the last IP infusion is required before blood samples for immunogenicity assessments can be drawn.

[e)] Viral Serology 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; HIV-1/HIV-2 Antibodies

[f)] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH

[g)] Not required if available in the subject's medical history; VWF multimers: additionally in case of thromboembolic events

[h)] At screening and in case of thromboembolic events

[i)] Blood group assessment major blood group (local laboratory) only if not available in the subject's medical history

[j)] Serum pregnancy test (in females of child-bearing potential if no urine sample is available)

[k)] The last post-infusion laboratory assessments coincidence with the initiation visit for prophylactic treatment. After the blood samples are drawn for laboratory assessment for the 96 h post infusion PK assessment, the subject receives the first IP infusion for prophylactic treatment (prophylactic treatment initiation visit).

[l)] Only needed for subjects without PK assessment prior to their first IP infusion in this study.

[m)] A steady state full PK analysis will be performed at the end of the study. 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), the 96 hr sampling can be omitted if not allowed by the dosinig interval.

[n)] Study treatment period is extended by 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. In this case, 12 month ± 2 weeks visit is to be considered as a follow-up visit, and EOS visit is to be performed once the subject can rollover into the continuation study, from 12 month ± 2 weeks to 15 month ± 2 weeks post prophylaxis initiation visit, as applicable.

Table 8b
Clinical Laboratory Assessments for pdVWF Switch Subject

Procedures/ Assessments	Screening Visit	Prophylaxis Initiation Visit	PK Assessment[k] (at prophylaxis dose #5-6)			Interval/Follow-Up Study Visits					PK Assessment[k] at Study Completion			Termination Visit
			Pre-infusion	Infusion	Post-infusion	1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion	Infusion	Post-infusion	Conducted at the 96 hour postinfusion PK Assessment
											12-15[l] month± 2 weeks			
Hematology [a]	X	X	X		X	X	X	X	X	X	X		X	X
Clinical Chemistry[b]	X	X	X		X	X	X	X	X	X	X		X	X
Coagulation Panel/PK assessment[c]	X	X	X		X	X	X	X	X	X	X		X	
Immunogenicity[d]	X	X				X	X	X	X	X	X			X
Viral Serology[e]	X													
Urinalysis[f]	X													
VWD Gene Mutational Analysis / HLA genotype analysis and Analysis of VWF multimers[g]	X													
sP-selectin and D-dimer	X[h]													
Blood Group[i]	X													
Pregnancy Test[j]	X													

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[a] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. Hematology assessments during PK assessments will be determined prior to IP infusion and 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours thereafter. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

[b] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin. Clinical chemistry will be determined prior to IP infusion and after 24 ± 2 h, 48 ± 2 hours and 72 ± 2 hours during the PK assessments. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

[c] Coagulation panel/PK assessment (also refers to IR pre/post dose assessments at prophy initiation visit and each follow-up visit): PT, INR and aPTT (only for screening), VWF:RCo, VWF:Ag, VWF:CB, FVIII:C,; during the PK assessment blood samples will be drawn 30 min prior PK infusion; once the PK infusion is completed 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 and VWF:RCo, VWF:CB, VWF:Ag, FVIII:C will be determined; for follow-up visits, IR samples will be drawn within 30 minutes pre-infusion and 30 ± 5 minutes post-infusion. During screening and in case of thromboembolic event VWF multimers and ADAMTS13 will be analyzed to judge on a possibly relatedness to UHMW fractions of the IP.

[d] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII –Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG. In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined. For switch subjects, the wash out period may be reduced to the time interval between their pdVWF prophy infusions.

[e] Viral Serology 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; HIV-1/HIV-2 Antibodies

[f] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH

[g] Not required if available in the subject's medical history; VWF multimers: additionally in case of thromboembolic events

[h] At screening and in case of thromboembolic events

[i] Blood group assessment major blood group (local laboratory) only if not available in the subject's medical history

[j] Serum pregnancy test (in females of child-bearing potential if no urine sample is available)

[k] A full steady state PK analysis will be performed. 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) , the 96 hr sampling can be omitted if not allowed by the dosinig interval.

[l] Study treatment period is extended by 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. In this case, 12 month ± 2 weeks visit is to be considered as a follow-up visit, and EOS visit is to be performed once the subject can rollover into the continuation study, from 12 month ± 2 weeks to 15 month ± 2 weeks post prophylaxis initiation visit, as applicable.

20.3.1 Laboratory Sampling for Surgical Bleeding

Table 9
Laboratory Sampling[a] for Surgical Bleeding

Procedures/ Assessments	**Surgical procedure**				**Post-Operative Day 7 Visit (± 1 day)**	**Post-Operative Day 14 Visit (± 2 day)**
	Priming Dose Procedures (12-24 hours prior to surgery)	**Loading Dose Procedures (≤ 3 hours prior to surgery)**	**Intraoperative**	**Postoperative (day 1 → end of perioperative IP treatment)[b]**		
Hematology[c]	X (w/o Differential)	X[d] (w/o Differential)		X (w/o Differential)	X	X
Clinical Chemistry[e]	X	X[d]			X	X
Coagulation panel[f]	X	X	X	X	X	X
VWF inhibitory and binding antibodies, antibodies to other proteins[g]	X	X	X if excessive or unexplainedbleeding	X	X	X
Urinalysis[h]					X	X
VWF Multimers[i]						
Anti VWF IgE antibody testing only in case of allergic reaction/ anaphylaxis						

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[a)] Blood draws are within 3 hrs prior to infusion start, expect that for the priming dose blood draw is within 30 minutes prior to infusion start. For coagulation panel, an additional 30 ± 5 minutes post-infusion blood draw is needed.
[b)] The assessments will be performed daily until perioperative IP treatment end (potentially multi-visits)
[c)] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.
[d)] Not required if sample already drawn at the time of the priming dose
[e)] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin.
[f)] Coagulation panel: VWF:RCo, VWF:Ag, FVIII:C PT INR and aPTT; in additiona to pre-infusion, 30 ± 5 minutes post infusion blood draw is needed.
[g)] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII – Neutralizing and Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG. In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined.
[h)] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH
[i)] VWD multimers and ADAMTS13 during the study only in case of thrombotic events

20.4 Contraceptive Methods for Female Subjects of Childbearing Potential

In this study, subjects who are women of childbearing potential must agree to utilize a highly effective contraceptive measure throughout the course of the study and for 30 days after the last administration ofIP. In accordance with the Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials (version 2014-09-15)[ii], birth control methods which may be considered as highly effective include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable[iii]
- Intrauterine device (IUD)[iii]
- Intrauterine hormone-releasing system (IUS) [iii]
- Bilateral tubal occlusion[iii]
- Vasectomised partner(s)[iii]
- Sexual abstinence during the entire study period

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

[ii] Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf.

[iii] Contraception methods that are considered to have low user dependency.

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19. [redacted]

20. [redacted]

21. [redacted]

22. SUMMARY OF CHANGES

Protocol 071301: Local Amendment 9 (Turkey): 2018 SEP 13

Replaces: Global Amendment 6: 2018 MAR 12

In this section, changes from the previous version of the Protocol, dated 2018 MAR 12, are described and their rationale is given.

1. **Throughout the document**
   Description of Change:
   Minor grammatical and/or administrative changes and/or rewording have been made.
   Purpose for Change: To improve the readability and/or clarity of the protocol.

2. **Synopsis (Study Design), Section 8.1**
   Description of Change:
   Added the wording about the possible up-to 3 months' extension of study participation for certain subjects.
   Purpose for Change: To add information about possible extension of study participation for certain subjects.

3. **Synopsis (Planned Duration of Subject Participation), Section 8.2**
   Description of Change:
   Added the note about the possible up-to 3 months' extension of study participation for certain subjects, and clarify that the planned duration of subject participation can therefore be extended to 18 months.
   Purpose for Change: To add information about possible extension of study participation for certain subjects.

4. **Synopsis (Secondary outcome measures), Section 8.3.2.1**
   Description of Change:
   Original text:
   Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 bleeding episodes during the 12-month prophylactic treatment with rVWF (vonicog alfa)
   New text:
   Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 bleeding episodes during the prophylactic treatment with rVWF (vonicog alfa)
   Purpose for Change: To remove the exact prophylactic treatment period as it can be extended beyond 12 month for certain subjects.

5. **Section 6.1**

Description of Change:
Updates were added to reflect the marketing authorization for Vonvendi in US and EU.
Purpose for Change: To provide updated marketing authorization for Vonvendi.

6. **Section 10.3.7**

Description of Change:
The detailed schedules of follow-up visits were removed as for certain subjects 12-month follow-up visit will be scheduled with the need of participation extension.
Purpose for Change: To remove the details to avoid confusion of possible 12-month follow-up visit.

7. **Section 10.3.9**

Description of Change:
End of study visit time was removed as for certain subjects the EOS visit can occur after 12 months with the need of participation extension.
Added the note about the possible up-to 3 months' extension of study participation for certain subjects
Purpose for Change: To add information about possible extension of study participation for certain subjects and to remove the details to avoid confusion of possible delayed EOS visit.

8. **Section 11.6, Section 12.10.2**

Description of Change:
Added the note about the possible up-to 3 months' extension of study participation for certain subjects.
Purpose for Change: To add information about possible extension of study participation for certain subjects.

9. **Section 20.2 Table 6a 6b, Section 20.3 Table 8a 8b**

Description of Change:
Added the footnote to reflect the possible up-to 3 months' extension of study participation for certain subjects.
Purpose for Change: To add note about possible extension of study participation for certain subjects.

10. **Section 20.2 Table 6a 6b, Section 20.3 Table 8a 8b**
Description of Change:
Some clarifications were made to the tables and the footnotes, to reflect the possible up-to 3 months' extension of study participation for certain subjects.
Purpose for Change: To add information about possible extension of study participation for certain subjects.

INVESTIGATOR ACKNOWLEDGEMENT

RECOMBINANT VON WILLEBRAND FACTOR (rVWF)

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

CLINICAL TRIAL PHASE 3

LOCAL AMENDMENT 9 (TURKEY): 2018 SEP 13

Replaces: GLOBAL AMENDMENT 6: 2018 MAR 12

OTHER PROTOCOL ID(s)
NCT Number: NCT02973087
EudraCT Number: 2016-001478-14
IND NUMBER: 013657

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT

RECOMBINANT VON WILLEBRAND FACTOR (rVWF)

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

CLINICAL TRIAL PHASE 3

LOCAL AMENDMENT 9 (TURKEY): 2018 SEP 13

Replaces: GLOBAL AMENDMENT 6: 2018 MAR 12

OTHER PROTOCOL ID(s)
NCT Number: NCT02973087
EudraCT Number: 2016-001478-14
IND NUMBER: 013657

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
[redacted], MD
[redacted]
Global Clinical Development Operations
Baxalta Innovations GmbH

CLINICAL STUDY PROTOCOL

PRODUCT: Recombinant Von Willebrand Factor (rVWF, vonicog alfa)

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 SHORT TITLE: rVWF IN PROPHYLAXIS

PROTOCOL IDENTIFIER: 071301

CLINICAL TRIAL PHASE 3

LOCAL AMENDMENT 10 (UNITED STATES): 2018 SEP 13

Replaces:
AMENDMENT 6: 2018 MAR 12

ALL VERSIONS:
Local (United States) Amendment 10: 2018 SEP 13
Local (Turkey) Amendment 9: 2018 SEP 13
Local (Czech Republic) Amendment 8: 2018 MAY 18
Local (Germany) Amendment 7: 2018 MAY 18
Amendment 6: 2018 MAR 12
Local (Czech) Amendment 5: 2017 AUG 08
Local (Germany) Amendment 4: 2017 AUG 04
Amendment 3: 2017 AUG 03
Amendment 2: 2016 DEC 15
Amendment 1: 2016 APR 08
Original: 2014 FEB 09

OTHER ID(s)
NCT Number: NCT02973087
EudraCT Number: 2016-001478-14
IND NUMBER: 013657

Study Sponsor(s):

Baxalta US Inc.
300 Shire Way
Lexington, MA 02421,US

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna, AUSTRIA

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted]
Global Clinical Development Operations
Baxalta Innovations GmbH

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (e.g. investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) and suspected unexpected serious adverse events (SUSARs) to the ECs.

ALL SAEs, INCLUDING SUSARs, ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT.

Bleeding events that meet seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) should be reported on the SAE eCRF and SAE Report form as an SAE.

Drug Safety contact information:

Baxalta Global Drug Safety fax number: [redacted]

OR

email: [redacted]

For definitions and information on the assessment of these events, refer to the following:

- Adverse Events (AEs), Section 12.1
- SAEs, Section 12.1.1.1
- SUSARs, Section 12.1.1.2
- Assessment of AEs, Section 12.1.2
- Safety Reporting, Section 12.1.2.3

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	Recombinant von Willebrand factor (rVWF, vonicog alpha)
Name(s) of Active Ingredient(s)	Recombinant von Willebrand factor (rVWF, vonicog alpha)
CLINICAL CONDITION(S)/INDICATION(S)	
Subjects with severe von Willebrand disease (VWD) (baseline VWF: Ristocetin cofactor activity (VWF:RCo) <20 IU/dL) requiring prophylactic treatment with coagulation factor replacement	
PROTOCOL ID	071301
PROTOCOL TITLE	A prospective, phase 3, open-label, international multicenter study on efficacy and safety of prophylaxis with rVWF in severe von Willebrand disease
Short Title	rVWF in prophylaxis
STUDY PHASE	Phase 3
PLANNED STUDY PERIOD	
Initiation	2017 OCT
Primary Completion	2019 Q4
Study Completion	2019 Q4
Duration	27 months
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
The purpose of this phase 3 study is to investigate the efficacy and safety, including immunogenicity, thrombogenicity and hypersensitivity reactions, as well as pharmacokinetics (PK), [redacted] and [redacted] of prophylactic treatment with rVWF (vonicog alfa) in adult subjects with severe VWD.	
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.	
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 FVIII activity	

Exploratory Objectives	
[redacted]	
STUDY DESIGN	
Study Type/ Classification/ Discipline	Efficacy and Safety
Control Type	No control
Study Indication Type	Prophylaxis and treatment of bleeding episodes
Intervention model	Single-group
Blinding/Masking	Open-label
Study Design	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, [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 (pdVWF switch subjects) will receive prophylactic treatment with rVWF (vonicog alfa) for a 12-month period (up to 15 months for the qualified subjects to rollover into the continuation study, if the continuation study start up is delayed beyond the completion of subject's 12-month visit).
Planned Duration of Subject Participation	Approximately 15 to 18* months * Study treatment period is extended by 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.
Primary Outcome Measure	
Efficacy • Annualized bleeding rate (ABR) for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa)	

Secondary Outcome Measures

Additional efficacy of prophylactic treatment with rVWF (vonicog alfa)

- ABR percent reduction success for OD subjects defined as at least 25% reduction of ABR for spontaneous (not related to trauma) bleeding episodes during rVWF (vonicog alfa) prophylaxis relative to the subject's own historical ABR during on-demand treatment
- ABR preservation success for pdVWF switch subjects 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 during prophylactic treatment with pdVWF
- Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 bleeding episodes during the 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
- Spontaneous ABR 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)

Safety

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

Pharmacokinetics (PK) and Pharmacodynamics (PD)

- PK parameters after a washout for on-demand 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 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 VWF:RCo, Von Willebrand factor antigen (VWF:Ag), Von Willebrand collagen binding activity (VWF:CB).
- PD parameters after a washout for on-demand subjects: C_{max}, T_{max}, and $AUC_{0-tlast}$ as measured in FVIII activity by the 1-stage clotting assay (FVIII:C).
- PK parameters at steady state for on-demand and switch subjects: area under the concentration versus time curve from 0 to end of the partial dosing interval ($AUC_{0-tau;ss}$), 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. PK parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.

- PD parameters at steady state for on-demand and switch subjects: $AUC_{0\text{-}tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$ as measured in FVIII actvitiy by the 1-stage clotting assay (FVIII:C). PD parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.
- Time course of FVIII clotting activity (FVIII:C) levels.

Exploratory Outcome Measures

[redacted]

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**Dosage form**: powder and solvent for solution for injection **Dosage frequency**: <u>Prophylactic Treatment</u> Subjects transitioning from on-demand treatment will receive twice weekly infusion with rVWF (vonicog alfa) at doses of 50 ± 10 IU/kg rVWF:RCo. Dosage may be individualized within this range based on: • available historical PK data • type and severity of bleeding episodes the subject has experienced in the past • monitoring of appropriate clinical and laboratory measures The starting dose can, after consultation with the Sponsor, be increased up to 80 U/kg if considered necessary to assure effective prophylaxis. Subjects switching from pdVWF prophylaxis treatment: the weekly dose (IU/kg) of rVWF (vonicog alfa) for each patient will be equivalent (± 10%) to the weekly VWF dose received during prophylactic treatment with pdVWF. The weekly dose should be divided into 2 infusions, 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. A once weekly dose regimen will be allowed after switch to rVWF (vonicog alfa) if the patient has been on a once weekly dose regimen with pdVWF. Dose and dose interval may, after consultation with the sponsor, be further individualized based on: • available historical PK data • type and severity of bleeding episodes the subject has experienced in the past • monitoring of appropriate clinical and laboratory measures <u>Treatment of Bleeding Episodes:</u> Dosage must be individualized based on the subject's weight, type and severity of bleeding episode and monitoring of appropriate clinical and laboratory measures. In general, an initial dose of 40-60 IU/kg VWF:RCo with or without 30-45 IU rFVIII [ADVATE, octocog alfa]/kg is recommended (rVWF:rFVIII ratio of 1.3:1: ± 0.2). In cases of major bleeding episodes, a dose of up to 80 IU/kg VWF:RCo may be infused. Subsequent doses, if necessary, will be administered with or without ADVATE (rFVIII, octocog alfa) to maintain VWF:RCo and FVIII levels for as long as deemed necessary by the investigator. **Mode of Administration:** intravenous

SUBJECT SELECTION	
Targeted Accrual	Approximately 22 adult subjects with severe VWD will be included to have ≥8 subjects in each cohort (OD and switch). A total of at least 5 type 3 VWD subjects will be followed for 12 months.
Number of Groups/ Arms/ Cohorts	Single-group

Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding:
    a. Type 1 (VWF:RCo <20 IU/dL) or,
    b. Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2M or,
    c. Type 3 (VWF:Ag ≤3 IU/dL).
2. Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.
3. For on-demand patient group, subject currently receiving on-demand treatment for whom prophylactic treatment is recommended by the investigator.
4. For pdVWF switch patient group, subject has been receiving prophylactic treatment of pdVWF products for no less than 12 months prior to screening.
5. For on-demand patient group, subject has ≥3 documented spontaneous bleeds (not including menorrhagia) requiring VWF treatment during the past 12 months.
6. Availability of records to reliably evaluate type, frequency and treatment of bleeding episodes during at least 12 months preceding enrollment. Up to 24 months of retrospective data should be collected if available. Availability of dosing and factor consumption during 12 months (up to 24 months) of treatment prior to enrollment is required for pdVWF switch subjects and is desired (but not a requirement) for on-demand subjects.
7. Subject is ≥18 years old at the time of screening and has a body mass index ≥15 but <40 kg/m^2.
8. If female of childbearing potential, subject presents with a negative blood/urine pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.
9. Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

Subjects who meet ANY of the following criteria are not eligible for this study:

1. The subject has been diagnosed with Type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD (e.g., qualitative and quantitative platelet disorders or elevated prothrombin time (PT)/international normalized ratio [INR] >1.4).
2. The subject is currently receiving prophylactic treatment with more than 5 infusions per week.
3. The subject is currently receiving prophylactic treatment with a weekly dose exceeding 240 IU/kg.
4. The subject has a history or presence of a VWF inhibitor at screening.

5. The subject has a history or presence of a FVIII inhibitor with a titer ≥0.4 Bethesda units (BU) (by Nijmegen modified Bethesda assay) or ≥0.6 BU (by Bethesda assay).
6. The subject has a known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins.
7. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
8. The subject has a medical history of a thromboembolic event.
9. The subject is human immunodeficiency virus (HIV) positive with an absolute Helper T cell (CD4) count <200/mm^3.
10. The subject has been diagnosed with significant liver disease per investigator's medical assessment of the subject's current condition or medical history or as evidenced by any of the following: serum alanine aminotransferase (ALT) greater than 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).
11. The subject has been diagnosed with renal disease, with a serum creatinine (CR) level ≥2.5 mg/dL.
12. The subject has a platelet count <100,000/mL at screening.
13. The subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to signing the informed consent.
14. The subject is pregnant or lactating at the time of enrollment.
15. Patient has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
16. The subject has participated in another clinical study involving another investigational product (IP) or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
17. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
18. The subject is scheduled for a surgical intervention.
19. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
20. The subject has a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
21. The subject is in prison or compulsory detention by regulatory and/or juridical order
22. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.

Delay criteria

1. If the subject presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) the screening visit will be postponed until the subject has recovered.

STATISTICAL ANALYSIS

Sample Size Calculation

Approximately 22 adult subjects with severe VWD will be included in the study. The aim is to have ≥8 subjects in each cohort (OD and switch). A total of at least five type 3 VWD subjects will be followed for 12 months. 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).[1]

Planned Statistical Analysis

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

The Safety Analysis Set will be composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

The Per-Protocol (PP) Analysis Set will be composed of subjects who are at least 70% compliant regarding the number of scheduled prophylactic infusions. Only subjects who meet all study entry criteria and who have no major protocol violations that might impact primary efficacy assessments will be included in the PP analysis set.

The Pharmacokinetic Full Analysis Set (PKFAS) will be composed of all subjects who received the PK infusion and who provided acceptable data for PK and PD analysis. Acceptable PK/PD data will be defined in the Statistical Analysis Plan.

Primary Outcome Measure:

No formal statistical hypothesis test is planned for the analysis. Spontaneous ABR while treated with rVWF (vonicog alfa) for each cohort, on demand and switch subjects, will be estimated using a negative binomial regression. The prior ABR for each cohort will be based on historical data collected from each enrolled subject. The two ABRs (observed on the study and historical) will be assessed 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 ABR ratio together with a two-sided, 95% confidence interval (CI) will be reported for each cohort.

The difference in on-study ABR relative to historical ABR will be summarized descriptively.

The primary efficacy analysis will be based on the FAS and will be summarized by the two cohorts: on-demand and switch subjects. As a supportive analysis, the same analysis will also be carried out on the per-PP analysis set.

Secondary Outcome Measures:

In general, data for secondary efficacy analysis will be summarized by the two cohorts: on-demand and switch subjects and when applicable overall. Mean, standard deviation, median, range, quartiles will be calculated for continuous endpoints. Proportions will be calculated for categorical endpoints. Confidence intervals at the 95% level will be provided when appropriate.

Additional efficacy of prophylactic treatment with rVWF (vonicog alfa):

The number and proportion of on-demand subjects with ABR percent reduction success (i.e. ≥ 25%) will be calculated together with a two-sided 95% CI for the proportion.

The number and proportion of pdVWF switch subjects with ABR preservation success will be reported together with the corresponding 95% two-sided CIs for the proportion.

The number and proportion of subjects with categorized spontaneous ABR (i.e. 0, 1-2, 3-5, more than 5 bleeds) will be reported descriptively.

Summary statistics for the total number of infusions, as well as average number of infusions per week will be provided. The total weight adjusted consumption of rVWF (vonicog alfa) during prophylactic treatment will be provided. If applicable, historical data on consumption of pdVWF prior to the study will be summarized as well.

The change in spontaneous ABR from the historical rate to that during the rVWF (vonicog alfa) prophylaxis period will be summarized by location of bleeding (GI, epistaxis, joint bleeding, menorrhagia, oral and other mucosa, muscle and soft tissue, etc.).

Pharmacokinetics (PK) and Pharmacodynamics (PD):

The following PK parameters, based on the initial PK assessment after a washout for on-demand subjects, will be listed and summarized descriptively for VWF:RCo, VWF:Ag and VWF:CB: IR, $T_{1/2}$, MRT, $AUC_{0-\infty}$, $AUC_{0\text{-tlast}}$, C_{max}, T_{max}, V_{ss}, and CL. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity (FVIII:C), based on the initial PK assessment after a washout for on-demand subjects will be assessed using C_{max}, T_{max}, and $AUC_{0\text{-tlast}}$. These PD parameters will be listed and summarized descriptively.

PK parameters at steady state ($AUC_{0\text{-tau;ss}}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$) for the partial dosing interval will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study for VWF:RCo, VWF:Ag and VWF:CB and summarized descriptively for subjects with the same dosing regimens. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity (FVIII:C) will be assessed using $AUC_{0\text{-tau;ss}}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$. These PD parameters will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study and will be summarized descriptively for subjects with the same dosing regimens.

For the on-demand subjects, the PK of VWF:RCo will be analyzed using a population PK approach to characterize the single and multiple dose pharmacokinetics, including associated variability, of VWF:RCo in the study population.

For the switch subjects, differences in $AUC_{0\text{-tau;ss}}$, $C_{max;ss}$, and $C_{min;ss}$ assessess shortly after reaching steady state and assessed at the end of the study will be assessed by ratio of geometric means and corresponding two-sided 95% confidence intervals for VWF:RCo, VWF:Ag, VWF:CB, and FVIII:C. 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.

Descriptive statistics will be used to summarize VWF:RCo, VWF:Ag, VWF:CB, and FVIII:C levels for each nominal time point on the PK curve. For all subjects activity/concentration vs. time curves will be prepared.

Safety:

Safety analysis will be performed overall and by the two cohorts: on-demand and switch subjects.

Treatment-emergent AEs (TEAEs) are defined as AEs with start dates on or after the first exposure to IP. Summaries of AEs will be based on TEAEs unless otherwise indicated.

Occurrence of AEs and serious AEs (SAEs) will be summarized descriptively, by system organ class and preferred term. The number and percentage of subjects who experienced AEs and SAEs, and the number of AEs and SAEs will be tabulated. In addition, the number of subjects who experienced AEs assessed as related to IP by the investigator, and the number of IP-related AEs will be tabulated. The number of patients with AEs by severity will be presented similarly.

A listing of all AEs will be presented by subject identifier, age, sex, preferred term and 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.

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 infusion, irrespective of being related or not related to treatment. Temporally associated AEs will be presented in summary tables.

Adverse events of special interest (AESI), such as hypersensitivity reactions and thromboembolic events, will be monitored throughout the study and statistical analysis will be conducted based on the search criteria (eg, standardized MedDRA queries [SMQ]) determined prior to database lock, and summarized.

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.

Clinically significant changes relative to baseline in vital signs and clinical laboratory parameters (hematology, clinical chemistry) will be reported.

4. TABLE OF CONTENTS

Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABR	Annualized bleeding rate
ADAMTS13	A Disintegrin And Metalloproteinase with a Thrombospondin type 1 motif, number 13
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the plasma concentration /time curve from time 0 to infinity
$AUC_{0-tau;ss}$	Area under the plasma concentration /time curve from time 0 to end of the partial dosing interval
$AUC_{0-tlast}$	Area under the plasma concentration /time curve from 0 to the last measurable concentration
aPTT	Activated partial thromboplastin time
B19V	Parvovirus B19
BP	Blood pressure
BU	Bethesda Unit
BUN	Blood urea nitrogen
BW	Body weight
CAM	Cell adhesion molecule
CBC	Complete blood count
CD4	Helper T cell
CHO	Chinese hamster ovary
CI	Confidence interval
Cl	Chloride
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max;ss}$	Maximum plasma concentration during the partial dosing interval at steady state
$C_{min;ss}$	Minimum plasma concentration during the partial dosing interval at steady state
CR	Creatinine
CTA	Clinical Trial Agreement
eCRF	Electronic case report form
DMC	Data monitoring committee
DIC	Disseminated intravascular coagulation

Abbreviation	Definition
DVT	Deep vein thrombosis
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
[redacted]	[redacted]
FAS	Full analysis set
FVIII	Factor VIII
FVIII:C	Factor VIII clotting activity
GCP	Good Clinical Practice
GI	Gastrointestinal
Glu	Glucose
HAMA	Human anti- mouse antibodies
HAV	Hepatitis A virus
HB	Hepatitis B
HBs	Hepatitis B surface
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
[redacted]	[redacted]
HRP	Horseradish peroxidase
IB	Investigator's brochure
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
INR	International normalized ratio
IP	Investigational product
IR	Incremental recovery
i.v.	Intravenous

Abbreviation	Definition
K	Potassium
k.o.	Knock out
LDH	Lactate Dehydrogenase
Na	Sodium
NMC	Non-medical complaint
NOAEL	No observed adverse effect level
MRI	Magnetic resonance imaging
MRT	Mean residence time
pdVWF	Plasma derived VWF product
pdVWF/FVIII	Plasma derived VWF product containing fractions of FVIII
PBAC	Pictorial Blood Assessment Chart
PCR	Polymerase Chain Reaction
PEF	Peak expiratory flow
PK	Pharmacokinetic
PKFAS	Pharmacokinetic Full Analysis Set
PKPPAS	Pharmacokinetic Per Protocol Analysis Set
PP	Per protocol
PT	Prothrombin time
Q1, Q3	Quartile
rFVIII	Recombinant factor VIII
rVWF	Recombinant von Willebrand factor
RBC	Red blood cell count
SAE	Serious adverse event
SAER	Serious adverse event report
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
[redacted]	[redacted]
SIC	Subject identification code
SMQ	Standardised MedDRA queries
sP-selectin	Soluble P-selectin
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Terminal phase half life
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack

Abbreviation	Definition
T_{max}	Minimum time to reach the maximum concentration
$T_{max;ss}$	Minimum time to reach the maximum concentration at steady state
TTP	Thrombotic thrombocytopenic purpura
ULMW	Ultra-large molecular weight
ULN	Upper limit of normal
V_{ss}	Volume of distribution at steady state
[redacted]	[redacted]
VTE	Venous thromboembolism
VWD	von Willebrand disease
VWF	Von Willebrand factor
VWF:Ag	Von Willebrand factor antigen
VWF:CB	Von Willebrand Factor collagen binding
VWF:RCo	Von Willebrand factor: Ristocetin cofactor activity
WBC	White blood cell

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

Baxalta US Inc. (hereafter referred to as Baxalta or sponsor) has developed a human recombinant von Willebrand Factor (rVWF, vonicog alpha), which is co-expressed with recombinant factor VIII (rFVIII) in a Chinese hamster ovary (CHO) cell line and separated during the subsequent downstream process. To address concerns regarding the risk of transmission of blood-borne pathogens that may be introduced by human plasma, no exogenously added raw materials of human or animal origin are employed in the cell culture, purification, or formulation of the final container product. The only proteins present in the final container product other than rVWF (vonicog alfa) are trace quantities of murine immunoglobulin (IgG, from the immunoaffinity purification), host cell (i.e., CHO) protein, rFurin (used to further process rVWF). rVWF (vonicog alfa) is intended for the treatment of von Willebrand disease (VWD).

rVWF (vonicog alfa) has been developed under the Baxalta internal code BAX111 and is used as investigational product (IP) in this study. rVWF (vonicog alfa) may be used with or without ADVATE (rFVIII, octocog alfa) for the treatment of bleeding episodes (see Section 8.6.4.4). See Section 8.6 for further information on the IPs and their usage in this study. A detailed description of rVWF (vonicog alfa) is also provided in the Investigator's Brochure (IB).

rVWF (vonicog alfa) was granted licensure in the United States in December 2015 under the brand name VONVENDI for the on-demand treatment and control of bleeding episodes in adults diagnosed with VWD and it has been available on the market in the US since 09 August 2016. In April 2018, VONVENDI was also granted licensure in the US by the FDA for an additional indication of perioperative management of bleeding in adults (age 18 and older) diagnosed with VWD. On 31st of August 2018, European Commission implemented the decision granting marketing authorization for VEYVONDI (vonicog alfa) for the treatment of haemorrhage and surgical bleeding and for the prevention of surgical bleeding in adults (age 18 and older) diagnosed with VWD, when desmopressin (DDAVP) treatment alone is ineffective or not indicated.

6.2 Clinical Condition/Indication

Von Willebrand Factor (VWF) is a large multimeric glycoprotein with a molecular weight that varies from 500 to 20,000 kDa. VWF is normally found in plasma and produced in the alpha-granules of platelets and in endothelial cell organelles known as the Weibel-Palade bodies. VWF mediates platelet adhesion and aggregation at sites of vascular injury, one of the key functions in primary hemostasis. VWF also serves to stabilize coagulation factor VIII (FVIII), where FVIII is an essential cofactor of secondary hemostasis, which leads to fibrin clot formation.[2] Qualitative and/or quantitative deficiencies of VWF lead to a highly variable bleeding diathesis known as VWD, the most common of the hereditary coagulation factor deficiencies. Penetrance of VWD is highly variable, with only a small fraction of mildly affected patients displaying clinical symptoms or a family history of a bleeding diathesis.

The current biochemical-based classification distinguishes disorders arising from partial quantitative (type 1), qualitative (type 2), or virtually complete (type 3) deficiencies of VWF. Up to 70% of VWD patients are diagnosed with type 1 VWD, which may also be associated with minor functional defects in the molecule. In general, patients with type 1 VWD display mild clinical symptoms. Approximately 20 to 30% of VWD patients are diagnosed with type 2 VWD. Type 2 VWD is further divided into 4 subtypes (A, B, N, and M), reflecting distinct classes of functional abnormalities. These defects result in abnormal functional and/or multimeric distribution patterns that facilitate their diagnosis. The bleeding diathesis is usually moderate and primarily affects the mucosal tissues. Type 2N VWD patients are sometimes misdiagnosed as mild hemophilia A. Finally, approximately 1% percent of VWD patients exhibit a total or near total absence of VWF, which is classified as type 3 VWD. The incidence of type 3 VWD is estimated at $0.5\text{-}1.0 \times 10^{6}$. This type is also associated with a very low FVIII level (typically <5%) because the VWF carrier function for FVIII is lost. Replacement of VWF alone stabilizes endogenous FVIII, resulting in hemostatic levels within several hours post-infusion. Published results from studies of a plasma-derived VWF (pdVWF) concentrate demonstrated an increase of FVIII at an approximate rate of 5.8 ± 1 IU dL^{-1} h^{-1}.[3] Type 3 VWD patients display severe hemorrhagic symptoms with bleeding predominantly in mucosal tissues, muscle and joints. All VWD patients, particularly those with type 2 or type 3 VWD, are at an increased risk for life-threatening bleeding episodes.

6.3 The Role of Prophylaxis in the Management of VWD

The goals of long term prophylaxis in VWD are to maintain VWF and FVIII at sufficient levels to reduce the frequency and duration of bleeding episodes, the need for red blood cell transfusions, and the risk of complications, such as arthropathy.[4] In contrast to hemophilia, routine prophylaxis is not as established in VWD, although prophylaxis for patients with severe VWD was in use in Sweden already during the 1950s.[5] In those early days of VWD treatment, plasma FVIII concentrates containing VWF fractions were applied for replacement therapy, which then were followed by plasma derived VWF products containing fractions of FVIII (pdVWF/FVIII).

A Swedish cohort including 37 patients with type 3 VWD under prophylactic median treatment of 11 years (range 2 to 45 years) was retrospectively analyzed.[6,7] The doses used for prophylaxis, given once weekly for at least 45 weeks per year, were calculated based on 12 to 50 IU/kg body weight (BW) of FVIII clotting activity (FVIII:C) which approximately corresponded to 24-100 IU/kg von Willebrand factor: Ristocetin cofactor activity (VWF:RCo) considering that mainly Haemate with a known VWF:RCo/FVIII:C ratio of about 2 was used. An escalation of doses from 1 to 3 dose levels was allowed depending on the frequency and severity of bleeding episodes. The results demonstrate that under long-term prophylaxis the number of bleeds could be reduced dramatically. Whereas the median value for bleeds per year was about 10 before prophylaxis this value could be reduced to less than 1 bleed per year during prophylaxis.

The benefit of prophylaxis for such indications was retrospectively also demonstrated in a cohort of Italian patients including type 3, 2A, 2M and type 1 patients. Prophylaxis was started after severe gastrointestinal or joint bleeding episodes and completely prevented bleeding episodes in 8 of these 11 patients and largely reduced the need of blood transfusions in the remaining 3. A regimen of 40 IU rVWF:RCo/kg was applied every other day or twice a week. A prospective study on prophylaxis, the PRO.WILL study, has been initiated in Italy.[8]

The results of a prospective study investigating the prophylaxis in children and young adults showed a significantly reduced bleeding frequency and bleeding score (3 vs. 0.07; 3 vs. 0. $p<0.001$) compared to the pre-prophylaxis values. The median dose was 40 (20-47) IU/kg VWF:RCo administered mainly twice weekly in 23 patients, 3 times a week in 7 patients and 4 times a week in 2 children.[9]

The VWD Prophylaxis Network initiated the VWD International Prophylaxis (VIP) trial to investigate the role of prophylaxis in patients with severe VWD including Type 1, 2, and 3. The dose of the factor replacement product was 50 IU /kgVWF:RCo.

The frequency of the dose depended on the type of bleeding and could be increased from once weekly to twice weekly or 3 times per week. For the treatment of menorrhagia the dose of 50 IU/kg VWF:RCo was given on the first day of menses for 2 cycles. The frequency could be increased to Day 1 and 2 for 2 cycles or to Day 1, 2, and 3 of menses.

The study contains both retrospective and prospective study components. Results from the retrospective study component were published, including 61 subjects on prophylactic regimen in the past 6 months prior to enrollment or subjects with a history of prophylaxis over at least 6 month.[10] Differences in annualized bleeding rates (ABR) within individuals (during prophylaxis – before prophylaxis) were significant for those with primary indications of epistaxis (P = 0.0005), joint bleeding (P = 0.002) and GI bleeding (P = 0.001). The difference in the group whose primary indication for treatment was abnormally heavy bleeding at menstruation (n = 4) was not significant (P = 0.25). The reduction of mucosal bleeding likely not only dependents on normal circulating levels of active VWF, but also on the presence of discrete concentrations of normal VWF inside the platelets and within endothelial matrices. The low subject number (n=4) and the treatment scheme for menorrhagia on Days 1, 2, and 3 of menses which might represent rather on-demand than prophylactic treatment may also account for the outcome in this study.

Results from the prospective study component were reported recently.[11] Eleven subjects completed the study. Six subjects had type 2A, and 5 subjects had type 3 VWD. Six subjects presented with epistaxis, 3 with GI bleeding, and 2 with joint bleeding. Seven subjects had dose escalation above the first level. Among the 10 subjects with evaluable bleeding log data, the use of prophylaxis decreased the median ABR from 25 to 6.1 (95% confidence interval [CI] of the rate difference: -51.6 to -1.7), and the median ABR was even lower (4.0; 95% CI: -57.5 to -5.3) when the subjects reached their final dosing level. The authors concluded that this was the first prospective study to demonstrate that prophylaxis with VWF concentrates is highly effective in reducing mucosal and joint bleeding rates in clinically severe VWD.

The results of the VIP study and previous investigations suggest that VWD patients with recurrent bleeding episodes and severe menorrhagia will benefit from a prophylactic VWF replacement therapy. There is evidence that up to 40% of patients with type 3 VWD experience joint bleeding which can lead to hemophilic arthropathy. Other potential indications for prophylaxis include patients with type 2A or 2B VWD with recurrent gastrointestinal bleeding, menorrhagia or frequent epistaxis.[4] Long-term prophylaxis for most patients with type 3 VWD and in some patients with type 1 or 2 VWD, depending on the pattern of bleeding, may be the treatment option of choice.

Although the main experience with long-term prophylaxis is with secondary prophylaxis, primary prophylaxis starting at young age is recommended to prevent arthropathy in patients with severe VWD.[12]

However, further studies are needed to develop evidence-based guidelines for prophylactic treatment in VWD.

6.4 Populations to be Studied

A total of approximately 22 eligible, adult subjects with severe VWD (baseline VWF:RCo <20 IU/dL) are planned to be enrolled. Two cohorts of patients will be included: patients currently receiving on-demand VWF treatment (OD subjects) and patients currently on prophylactic treatment with pdVWF (pdVWF switch subjects), and the aim is to have ≥8 subjects in each of the 2 cohorts, with a total of at least 5 type 3 VWD subjects followed for 12 months. Enrolled subjects (i.e., subjects who have signed the informed consent form) will be eligible to participate in the study if they meet all of the inclusion criteria (see Section 9.1) and none of the exclusion criteria (see Section 9.2).

6.5 Findings from Nonclinical and Clinical Studies

The following summarizes the key findings from relevant nonclinical studies as well as from the completed clinical studies **070701** (Phase 1 pharmacokinetics [PK] and safety in VWD), **071001** (Phase 3 safety and efficacy in the treatment of bleeding episodes in VWD), **071101** (Phase 3 efficacy and safety in VWD subjects undergo elective surgical procedures), **071104** (Phase 1 safety and PK in hemophilia A), and **071401** (Phase 3, expanded access in a single subject with VWD). Potential risks and efficacy of rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) are summarized in the following sections. For additional information on nonclinical and clinical Phase 1 results refer to the rVWF (vonicog alfa) IB.

6.5.1 Findings from Nonclinical Studies

6.5.1.1 Primary Pharmacodynamics

Efficacy of rVWF (vonicog alfa) combined with ADVATE (rFVIII, octocog alfa) was shown in VWD animal models, which have also low endogenous FVIII levels. Time to occlusion and stable thrombus formation was assessed in the carotid occlusion model in VWD mice. The results demonstrated that rVWF (vonicog alfa) in combination with ADVATE (rFVIII, octocog alfa) acted efficiently in a dose-dependent manner and had higher efficacy than rVWF (vonicog alfa) alone or plasma derived (pd)VWF. These results were confirmed in an additional study assessing blood loss and survival in a tail tip bleeding model in VWD mice. In a VWD dog, rVWF (vonicog alfa) stabilized canine FVIII in the circulation and significantly reduced the bleeding time.

6.5.1.2 Safety Pharmacology

The anaphylactoid and thrombogenic potential of the co-infusion of ADVATE (rFVIII, octocog alfa) and rVWF (vonicog alfa) and the co-infused product's effects on blood pressure, cardiac and respiratory function and parameters of coagulation activation were investigated in 4 in vivo studies in different animal models. Safety pharmacology studies in rats, guinea pigs, rabbits, and dogs revealed no risks for anaphylactoid and thrombogenic potential of ADVATE (rFVIII, octocog alfa) in combination with rVWF (vonicog alfa). All observations in safety pharmacology studies are considered to lie within the biological variability of animal models or occurred due to known species-specific anaphylactoid effects of excipients.

6.5.1.3 Pharmacokinetics

Pharmacokinetic studies of both rVWF (vonicog alfa) alone and combined with human rFVIII (rVWF+ADVATE) were conducted in VWD mice, VWD dogs, VWD pigs, rats, and cynomolgus monkeys. Human rVWF (vonicog alfa) stabilized the endogenous FVIII in VWD mice, VWD pigs, and VWD dogs. Furthermore, the hypotheses that the area under the curve (AUC) with rVWF alone and rVWF+ADVATE is not inferior to the AUC with pdVWF (Haemate P) was tested and confirmed statistically in normal rats. The PK characteristics of ADVATE (rFVIII, octocog alfa) were not affected by co-administration of rVWF (vonicog alfa) in cynomolgus monkeys. The PK data in the FVIII knock out (k.o.) mice model are inconclusive and might not be relevant for the clinical situation. However, a stabilizing effect of VWF on FVIII could be shown in a double k.o. model in a dose dependent manner.

6.5.1.4 Toxicology

Single dose toxicity studies were conducted in C57BL/6J-mice, VWD mice, rats, rabbits, and cynomolgus monkeys. Rats, rabbits, and cynomolgus monkeys showed no signs of toxicity. Signs of microthrombosis, an exaggerated pharmacological effect, were observed in mice. Mice are not capable of sufficiently cleaving the rVWF (vonicog alfa) subunit as murine disintegrin and metalloproteinase with a thrombospondin type 1 motif, number 13 (ADAMTS13) does not decrease the ultra-large molecular weight multimers of rVWF (vonicog alfa).[13] The observed symptoms of microthrombosis are interpreted as a species-specific exaggerated pharmacological effect. Studies evaluating the safety of repeated administration of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) (daily over 14 days) were performed in a rodent (rat) and non-rodent (cynomolgus monkey) species. Reversible signs of exaggerated pharmacological effects (regenerative anemia, thrombocytopenia, and treatment-related histopathologic changes in the heart, liver, and spleen) were observed in rats that were administered 1400 U VWF:RCo/kg /day + 1080 IU ADVATE/kg/day intravenously once daily for 14 days.

Also, these findings are interpreted as a species-specific exaggerated pharmacological effect due to the low susceptibility of human rVWF (vonicog alfa) to cleavage by rodent ADAMTS13.[13] No toxicologically relevant changes were evident for clinical observations, body weight, feed consumption, ophthalmology, urinalysis, coagulation, and serum chemistry parameters, platelet aggregation, and gross pathology. rVWF (vonicog alfa) combined with ADVATE (rFVIII, octocog alfa) was well tolerated in cynomolgus monkeys after daily intravenous (i.v.) (bolus) administration of 100 U VWF:RCo/kg rVWF (vonicog alfa) combined with 77 IU/kg ADVATE (rFVIII, octocog alfa) over a period of 14 days. No adverse effects could be detected in this species. There were no signs of hemolysis, thrombosis, or thrombocytopenia after repeated intravenous application of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa). Therefore, 100 U VWF:RCo/kg/day rVWF (vonicog alfa) with or without 77 IU/kg ADVATE (rFVIII, octocog alfa) was considered the no observed adverse effect level (NOAEL) in this study, which was the highest dose tested. Anti-drug antibodies, however, were formed in both species and resulted in a significant reduction in drug exposure after 14 applications as compared to a single application. These antibodies substantially reduced the systemic exposure to the test substance as compared to a single dose administration. No adverse effects due to antibody formation were observed in both species.

rVWF (vonicog alfa) combined with ADVATE (rFVIII, octocog alfa) was well tolerated locally and no genotoxic potential was evident after 2 in vitro and 1 in vivo genotoxicity study. A study on the influence of co-administration of VWF and ADVATE (rFVIII, octocog alfa) on the immunogenicity of ADVATE (rFVIII, octocog alfa) in 3 different hemophilic mouse models (E17 hemophilic Balb/c mice, E17 hemophilic C57BL/6J mice, and E17 hemophilic human F8 transgenic mice) showed that rVWF (vonicog alfa) does not negatively impact the immunogenicity of ADVATE (rFVIII, octocog alfa) in any of the three different hemophilic mouse models.

6.5.2 Findings from Clinical Studies

The clinical safety, efficacy and PK were assessed in 4 completed trials: one phase 1 study (**070701)**) and two phase 3 studies (**071001** and **071101**) that enrolled patients with VWD; one phase 1 study (**071104**) that enrolled patients with hemophilia A. Details on study design, populations enrolled, and safety and efficacy outcomes of the phase 1 studies are presented in Section 6.5.2.1 and Section 6.5.2.2, the phase 3 study in Section 6.5.2.3, and the phase 3 surgery study in Section 6.5.2.4. Information on a single subject with VWD in Study **071401** is presented in Section 6.5.2.5.

6.5.2.1 Study 070701

Phase 1 clinical study **070701** was a multicenter, controlled, randomized, single-blind, prospective 3-step, dose escalation study to investigate safety, tolerability, and PK of rVWF (vonicog alfa) combined at a fixed ratio with ADVATE (VWF:RCo/FVIII:C of 1.3 ± 0.2:1) in adults with severe VWD.[14] Subjects were enrolled in sequential cohorts in a dose escalating manner: Cohort 1, 2, and 3 received a single intravenous infusion of rVWF:ADVATE at the following doses: 2 IU/kg VWF:RCo (Cohort 1), 7.5 IU/kg VWF:RCo (Cohort 2), and 20 IU/kg VWF:RCo (Cohort 3). Subjects in Cohort 4 received a single intravenous infusion of rVWF:ADVATE and pdVWF/ADVATE at 50 IU/kg VWF:RCo in random order.

The primary endpoint was the tolerability and safety after single dose injections of rVWF:ADVATE at 2, 7.5, 20, and 50 IU/kg VWF:RCo for up to 30 days after the last IP infusion. The data generated in this phase 1 study suggest that rVWF:ADVATE up to the highest investigated dose of 50 IU/kg VWF:RCo is well tolerated and safe in adults with severe VWD. No thrombogenic risk or thrombotic thrombocytopenic purpura (TTP)-like syndrome was observed, and no neutralizing antibodies to VWF or FVIII were identified. There were no deaths or other serious adverse reactions, and no infusions were interrupted or stopped due to an AE. Overall, the reported AE profile was similar between the recombinant and plasma-derived concentrates.

Secondary endpoints were the PK assessment of VWF:RCo, von Willebrand factor antigen (VWF:Ag) and multimeric composition of rVWF (vonicog alfa) as well as FVIII:C at standardized time points after single injections of rVWF:ADVATE and pdVWF:FVIII.

The median VWF:RCo terminal half-life ($T_{1/2}$) of rVWF (vonicog alfa) at the 50 IU/kg dose was 16 hours. $T_{1/2}$ with pdVWF:FVIII at the same dose level appeared shorter at 12.58 hours, however, the limits of the 90% CI were similar (11.73 to 17.7 hours vs. 11.87 to 18.03 hours). The median $T_{1/2}$ of VWF:RCo were shorter with the lower investigated doses: 7.13 hours and 13.23 hours with the 7.5 IU/kg and 20 IU/kg doses, although these data were derived from a much smaller number of subjects.

In consequence of the missing ADAMTS13 cleavage, ultra-large molecular weight (ULMW) multimers are contained in the rVWF (vonicog alfa) final product. The immediate cleavage of these ultra-large multimers by ADAMTS13 upon release into the circulation could be demonstrated applying sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE)/Immunoblot with polyclonal anti-VWF antibodies to detect the resulting rVWF (vonicog alfa) subunit cleavage fragments.

Overall the data generated in this phase 1 study suggest that rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) is well tolerated and safe in adults with severe VWD.

6.5.2.2 Study 071104

This study was a prospective, uncontrolled, non-randomized, multicenter proof of concept study to assess safety and PK of the addition of rVWF (vonicog alfa) to ADVATE (rFVIII, octocog alfa) treatment in 12 evaluable subjects with severe hemophilia A. All subjects underwent 3 PK analyses: the first after infusion with ADVATE (rFVIII, octocog alfa) alone, the second after infusion with ADVATE (rFVIII, octocog alfa) plus 10 IU/kg rVWF (vonicog alfa) and the third after infusion with ADVATE (rFVIII, octocog alfa) plus 50 IU/kg rVWF (vonicog alfa).

The PK analysis was performed at intervals of approximately 8 to 14 days. Before each infusion for PK assessment, there was a wash-out period of at least 5 days and the subjects were not actively bleeding.

Primary outcome measures indicate that co-administration of rVWF (vonicog alfa) slightly sustain ADVATE activity with the highest observed ADVATE (rFVIII, octocog alfa) half-life of 13.74 h (CI 11.44 to 16.52) after co-infusion of 50 IU/kg ADVATE plus 50 IU/kg rVWF:RCo.

The highest improvement in ADVATE (rFVIII, octocog alfa) circulating half-life was observed in subjects with VWF:Ag levels below 100% which indicates an association between baseline VWF:Ag levels and ADVATE (rFVIII, octocog alfa) half-life increase.

No treatment related AEs or SAEs were reported. No subject withdrew due to an AE and there were no deaths. No binding antibodies to VWF, CHO, and rFurin were detectable in the confirmatory assay and no signs of a hypersensitivity to rVWF (vonicog alfa) or ADVATE (rFVIII, octocog alfa) antigen were observed. Laboratory values over time did not indicate any potential safety risk for hemophilia A patients treated with rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) in combination.

In summary, the data indicate that rVWF (vonicog alfa) co-administered with ADVATE (rFVIII, octocog alfa) up to the highest dose of 50 IU/kg VWF:RCo is well tolerated and safe in hemophilia A patients.

6.5.2.3 Study 071001

This was a phase 3, multicenter, open-label, part-randomized clinical study to assess the PK, safety, and efficacy of rVWF:rFVIII and rVWF in the treatment of bleeding episodes in adult subjects with severe type 3 and severe non-type 3 VWD.[15] A total of 49 subjects were enrolled (signed informed consent) and screened, 18 subjects were randomized (randomization only applies to Arm 1[PK50 with treatment of BE] and Arm 2 [PK50 only] see below), 37 subjects were treated with IP (all study arms), and 30 subjects completed the study.

The study consisted of 2 parts (Part A and Part B). Part A consisted of PK assessments alone (Arm 2: PK50 only [without treatment of bleeding episodes]), or PK assessments (Arm 1: PK50 and Arm 3: PK80) plus on-demand treatment period(s) of 6 months for bleeding episodes, or on-demand treatment for bleeding episodes only (Arm 4). Except for subjects in arm 2 who completed study after second PK assessment, subjects receiving treatment for PK assessments and/or bleeding episodes in Part A were to be entered into Part B to continue on-demand treatment for bleeding episodes for 6 additional months for a total of 12 months in the study.

The primary outcome measure was the number of subjects with "treatment success" (extent of control of bleeding episodes), which was defined as a mean efficacy rating score of <2.5 for a subject's IP-treated bleeding episodes during the study. The rate of subjects with treatment success was 100% (Clopper-Pearson exact 90% CI: 84.7 to 100.0) for bleeds where the assessments were made prospectively and excluding GI bleeds. Sensitivity analyses confirmed the results of the primary analysis.

Crossover results at 50 IU/kg VWF:RCo showed that the PK profile for rVWF (vonicog alfa) VWF:RCo was independent of administration alone or with rFVIII (ADVATE, octocog alpha) ($T_{1/2}$: 19.4 hours for rVWF and 16.6 hours for rVWF:rFVIII; IR: 1.8 U/dL per IU/kg infused for both rVWF and rVWF:rFVIII; mean residence time (MRT): 26.7 hours for rVWF and 25.2 hours for rVWF:rFVIII). FVIII levels increased substantially with a median peak at 24 hours of 111.0 U/dL for rVWF:rFVIII and 86.0 U/dL after rVWF alone, indicating that rVWF (vonicog alfa) induces a sustained increase in endogenous FVIII activity. The rVWF (vonicog alfa) PK profile was comparable at 50 IU/kg and 80 IU/kg VWF:RCo, and repeated PK at 80 IU/kg VWF:RCo showed close agreement between pretreatment and end-of-study results.

Further analysis of the PK data from the **071001** study supports the initial use of 50 IU/kg twice weekly for prophylaxis dosing in the present study for those subjects who are moving from on-demand to prophylaxis. Using 50 IU/kg for PK measurements, subjects in the **071001** study exhibiting a $T_{1/2}$ for rVWF of 14, 16, or 19 hours had rVWF plasma concentrations at 72 hours after administration of 2.55, 4.01, and 6.49% above baseline, respectively, and plasma concentrations at 96 hours after administration of 0.78, 1.40, and 2.71% above baseline, respectively. In this context it should be noted that subjects in the present study who have significant spontaneous bleeding while on twice weekly prophylaxis will have their regimen increased to 3 times per week based on clear criteria for different bleeding locations (for details see Section 8.6.4.3.1). Subjects in the present study who are switching from prophylaxis with a pdVWF product will begin on rVWF (vonicog alfa) using their same weekly total dose in IU/kg VWF:RCo used during their pdVWF prophylaxis divided into twice weekly infusions (for details see section 8.6.4.3).

A total of 125 AEs occurred in 25/37 (67.7%) subjects (62/318 infusions [19.5%]) during or after infusion with IP. Of these, 116/125 were non-serious (all mild or moderate; none were severe), and 9 SAEs were reported in 7 subjects. Of 125 total AEs, 38 were temporally associated with IP; 8 AEs were considered causally related to IP: 6 non-serious related AEs (tachycardia, infusion site paraesthesia, electrocardiogram [ECG] t-wave inversion, dysgeusia, generalized pruritis, and hot flush) occurred in 4 subjects, and 2 related SAEs (chest discomfort and increased heart rate) occurred in 1 subject. No deaths occurred during this study.

None of the subjects developed anti-VWF or anti-FVIII neutralizing antibodies and no binding antibodies to VWF or rFurin, or antibodies against CHO protein or anti-Murine IgG were observed. No clinical or subclinical signs or symptoms of a thrombogenic event were observed in this study. Following an initial increase in ultralarge VWF multimers after administration of rVWF (vonicog alfa), a notable decrease in the proportion of large VWF multimers occurred between 12 and 24 hours post infusion, due to degradation by the endogenous ADAMTS13 followed by a continued decline until the end of the 96-hour follow-up period.

Overall, the data support the safe and effective use of rVWF (vonicog alfa) with or without rFVIII (ADVATE, octocog alpha) in the treatment of bleeds in patients with VWD.

6.5.2.4 Study 071101

This was a phase 3, prospective, open-label, multicenter clinical study to evaluate efficacy and safety of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) in elective surgical procedures in adult subjects with severe VWD. A total of 24 subjects were enrolled (signed informed consent) and screened, 15 subjects were treated with rVWF (vonicog alfa), and 15 subjects completed the study.

Eleven subjects underwent a PK assessment by infusion of 50 ± 5 IU/kg rVWF:RCo at an infusion rate of up to 4 mL/min. 12 to 24 hours before surgery, subjects received a dose of 40 to 60 IU/kg rVWF:RCo. Within 3 hours prior to surgery, the subject's FVIII:C levels were assessed with a target of 30 IU/dL for minor and oral surgeries and 60 IU/dL for major surgeries. Within 1 hour prior to surgery, subjects received a dose of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) (depending on the target FVIII:C levels at the 3 hour assessment). VWF and FVIII IR and $T_{1/2}$ for each subject, when known, were used to guide the initial dose and subsequent doses.

The primary outcome measure was the overall assessment of hemostatic efficacy assessed by the investigator (hemophilia physician) 24 hours after last perioperative IP infusion or at completion of day 14 visit, whichever occurred earlier, and was summarized by the percentage of subjects in each efficacy category ("excellent", "good", "moderate" and "none"). Point estimate and corresponding 90% two-sided exact CI was calculated for the rate of subjects with an overall assessment of hemostatic efficacy. All 15 subjects treated with rVWF (vonicog alfa) (with or without ADVATE) for major (10), minor (4), and oral (1) elective surgical procedures had overall hemostatic efficacy ratings of "excellent" or "good". Most (73.3%) subjects had "excellent" overall hemostatic efficacy ratings; of these, 7 underwent major surgery and 4 underwent minor surgery. The remaining 26.7% subjects had "good" overall hemostatic efficacy ratings: 3 underwent major surgery and 1 underwent oral surgery. All 8 subjects with VWD Type 3, the subtype classified as absolute VWF deficiency, had overall hemostatic efficacy ratings of "excellent" (87.5%) or "good" (12.5%).

Intraoperative hemostatic efficacy ratings were also rated as "excellent" or "good" for all 15 treated subjects. Most (86.7%) subjects had "excellent" intraoperative hemostatic efficacy ratings; of these, 8 underwent major surgery, 4 underwent minor surgery, and 1 underwent oral surgery. Two (13.3%) subjects who underwent major surgery had "good" intraoperative hemostatic efficacy ratings. Intraoperative hemostatic efficacy was rated as "excellent" or "good" for all subjects with VWD Type 3: "excellent" for 7 (87.5%) subjects and "good" for 1 (12.5%) subject.

Only 1 subject received an intraoperative dose of rVWF (18.1 IU/kg) and ADVATE (8.1 IU/kg). The median daily postoperative weight-adjusted dose of rVWF (vonicog alfa) (with or without ADVATE) was 23.5 IU/kg on postoperative Day 1 (n=3) and 25.5 IU/kg on postoperative Day 14 (n=2). In subjects treated with rVWF:ADVATE, the daily postoperative weight-adjusted dose was 16.9 IU/kg rVWF and 7.6 IU/kg ADVATE on postoperative Day 1 (n=1) and decreased to 50.8 IU/kg rVWF and 7.6 IU/kg ADVATE on postoperative Day 7 (n=1). For subjects treated with rVWF alone, the median weight-adjusted dose (Q1, Q3) of rVWF was 35.4 IU/kg on postoperative Day 1 (n=2) and decreased to 23.7 IU/kg on postoperative Day 7 (n=4) and 25.5 IU/kg on postoperative Day 14 (n=2).

A total of 11 subjects were evaluated for PK in the study. As expected, postinfusion increases in concentrations of VWF:RCo, VWF:Ac, VWF:Ag, and VWF collagen binding (VWF:CB) were observed. Mean values for VWF:RCo were as follows: AUC0-∞/dose was 37.50 hours*IU/dL per IU/kg infused; AUC0-72h/dose was 34.08 hours*IU/dL per IU/kg infused; T1/2 was 17.83 hours; MRT was 24.32 hours; CL was 0.03117 dL/hour/kg; and volume of distribution at steady state (Vss) was 0.6837 dL/kg. Median values for VWF:RCo were as follows: AUC0-∞/dose was 32.94 hours*IU/dL per IU/kg infused; AUC0-72h/dose was 31.70 hours*IU/dL per IU/kg infused; T1/2 was 14.62 hours; MRT was 21.80 hours; CL was 0.03036 dL/hour/kg; and Vss was 0.7078 dL/kg. The VWF:RCo activity was consistent with that previously observed in clinical studies 071001 and 070701.

rVWF (vonicog alfa) was safe and well tolerated in adults with severe VWD undergoing major, minor, and oral elective surgical procedures. Of the 12 total treatment-emergent AEs (TEAEs) that occurred during the study, 2 deep vein thrombosis events (1 non-serious and 1 serious, as a part of one case) reported in one subject, who underwent total hip replacement surgery and who had concurrent condition of obesity, was assessed by the sponsor as possibly causally-related to study treatment. None of the TEAEs were either a severe allergic or hypersensitivity reaction or developed due to a severe allergic reaction.

One subject with VWD Type 3 who had an intraoperative transfusion of packed red blood cells during total knee replacement surgery tested positive for binding antibodies to VWF on postoperative Day 7 through study completion. No subjects developed neutralizing antibodies to rFVIII or binding antibodies to CHO, rFurin, or murine IgG.

In summary, the data support the safe and effective use of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) in achieving intra- and post-operative hemostasis in adult subjects with severe VWD undergoing major, minor, and oral elective surgical procedures.

6.5.2.5 Study 071401: Single Subject with von Willebrand Disease

One subject who exhibited allergic reactions to currently marketed pdVWF products was treated in the single-subject study **071401** with rVWF (vonicog alfa) only for the bleed treatment of continued hematuria, and for biopsy and surgical resection of a left-kidney mass.

For the initial rVWF (vonicog alfa) infusion, the subject received a test dose of 5% of the total dose of 60 IU/kg rVWF:RCo at an infusion rate of 1 mL/min. After a 10 to 15-minute observation period, no adverse symptoms or signs were noted and the subject received the remaining 95% of the total dose. The subject was monitored for any signs of an allergic reaction, and none were noted. Treatment with rVWF (vonicog alfa) every 12 to 24 hours was to continue at the discretion of the investigator based on VWF levels and clinical symptomatology. The subject had an excellent response and recovery, which allowed for daily dosing of rVWF (vonicog alfa) and, within 24 hours, the subject's bleeding had stopped. Daily dosing of rVWF (vonicog alfa) was maintained and the subject received his last dose on [redacted].

The subject also received rVWF (vonicog alfa) for 7 days for prophylaxis for surgery (surgical resection of a left-kidney mass). The subject experienced no hemorrhagic complications and no AEs that were considered related to the use of rVWF (vonicog alfa).

6.6 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

Current treatment of VWD patients relies on desmopressin and VWF products manufactured from pooled human plasma. Human VWF produced by recombinant technology could offer a new perspective in treatment of VWD. The benefit for the individual subject is anticipated to be significant during this clinical study. He/she may benefit from a product that minimizes excessive FVIII administration and thus allowing individualized dosing of VWF at optimal levels. Variations in VWF multimeric composition may lead to variability with respect to treating or preventing bleeds in VWD subjects, especially mucosal bleeds which are especially problematic. rVWF (vonicog alfa) product manufactured by Baxalta consistently contains ULMW VWF multimers due to the fact that the product has not been exposed to ADAMTS13.

The initial presence of these ULMW VWF multimers, which are subsequently cleaved by the subject's endogenous ADAMTS13, may result in improved platelet and collagen binding and therefore provide more predictable treatment outcomes.

By using a recombinant product, the risk of transmission of adventitious agents and other blood-borne pathogens associated with the use of products of human or animal origin has been eliminated. At this stage of product development, the key societal benefit is a better understanding of advanced treatment options for VWD and enhanced product availability.

These benefits outweigh the following identified or potential risks of rVWF (vonicog alfa):

- allergic-type hypersensitivity reactions as with any intravenous protein product
- the occurrence of thromboembolic events
- the development of neutralizing antibodies to VWF

Refer to the IB for further details on benefits and risks of the IP.

6.7 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996, with Addendum E6(R2) dated Nov 2016 EMA/CHMP/ICH/135/1995), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives 2001/20/EC and 2005/28/EC, the Declaration of Helsinki and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

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

7.2 Primary Objective

The primary objective of this study is to prospectively evaluate the 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.

7.3 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 FVIII activity

7.4 Exploratory Objectives

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

8. STUDY DESIGN

8.1 Overall Study Design

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

Subjects transitioning from on-demand treatment (OD subjects) or subjects switching from prophylactic treatment with pdVWF (pdVWF switch subjects) will receive prophylactic treatment with rVWF (vonicog alfa) for a 12-month period (up to 15 months for the qualified subjects to rollover into the continuation study, if the continuation study start up is delayed beyond the completion of subject's 12-month visit). The dose will be 50 ± 10 IU/kg rVWF twice weekly for OD subjects or will be based on their prior pdVWF dose for pdVWF switch subjects, and 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 Section 8.6.4.3).

The overall duration of prophylactic treatment with rVWF per subject will be at least 12 up to 15* months.

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 Section 8.6.4.4.2).

The overall study design is illustrated in Figure 1.

* Study treatment period is extended by 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.

8.2 Duration of Study Period(s) and Subject Participation

The overall duration of the study is approximately 27 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The subject participation period is approximately 15 to 18* months from enrollment to completion (i.e, last study visit), unless the subject is prematurely discontinued.

* Study treatment period is extended by 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.

8.3 Outcome Measures

8.3.1 Primary Outcome Measure

8.3.1.1 Efficacy

- Annualized bleeding rate (ABR) for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa)

8.3.2 Secondary Outcome Measures

8.3.2.1 Additional efficacy of Prophylactic Treatment with rVWF (vonicog alfa)

- ABR percent reduction success for OD subjects defined as at least 25% reduction of ABR for spontaneous (not related to trauma) bleeding episodes during rVWF (vonicog alfa) prophylaxis relative to the subject's own historical ABR during on-demand treatment
- ABR preservation success for pdVWF switch subjects 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 during prophylactic treatment with pdVWF
- Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 bleeding episodes during the 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
- Spontaneous ABR 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)

8.3.2.2 Safety

- AEs: incidence, severity, causality
- Thromboembolic events
- Hypersensitivity reactions
- Development of neutralizing antibodies to VWF and FVIII
- Development of total binding antibodies to VWF and FVIII

- Development of binding antibodies to CHO proteins, mouse immunoglobulin G (IgG) and rFurin
- Clinically significant changes in vital signs and clinical laboratory parameters relative to baseline

8.3.2.3 Pharmacokinetics (PK) and Pharmacodynamics (PD)

- PK parameters after a washout for on-demand subjects: incremental recovery (IR), $T_{1/2}$, 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 VWF:Rco activity, VWF:Ag, VWF:CB activity.
- PD parameters after a washout for on-demand subjects: C_{max}, T_{max}, and $AUC_{0-tlast}$ as measured in FVIII activity by the 1-stage clotting assay (FVIII:C).
- PK parameters at steady state for on-demand and switch subjects: area under the concentration versus time curve from 0 to end of the partial dosing interval ($AUC_{0-tau;ss}$), 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. PK parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.
- PD parameters at steady state for on-demand and switch subjects: $AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$ as measured in FVIII activity by the 1-stage clotting assay. PD parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.
- Time course of FVIII clotting activity (FVIII:C) levels.

8.3.3 Exploratory Outcomes Measures

8.3.3.1 [redacted]

8.3.3.2 [redacted]

8.3.3.3 [redacted]

8.3.3.4 [redacted]

8.4 Randomization and Blinding

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

8.5 Study Stopping Criteria

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 (eg, 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.

The sponsor ultimately 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.

8.6 Investigational Product(s)

8.6.1 Packaging, Labeling, and Storage

8.6.1.1 rVWF (Recombinant von Willebrand Factor, vonicog alfa)

rVWF (vonicog alfa) will be packaged in boxes with 2 glass vials, one containing the rVWF powder, and the second vial containing the diluent (water for injection). Further details are provided in the IB and Pharmacy Manual. The rVWF label will include, at a minimum, the actual VWF:RCo potency and the date of expiration.

rVWF (vonicog alfa) is a powder that should be stored refrigerated (2-8°C [36-46°F]) . Deviations from the storage condition have to be communicated and followed up with the sponsor. Inadequately stored product will have to be placed in quarantine and may only be used after written IP administration authorization by the sponsor. After removal of the product from the refrigerator the product must not be returned to the refrigerator. The reconstituted product has to be used immediately (at least within 3 hours). rVWF (vonicog alfa) must not be used beyond the expiration date printed on the vial label. Avoid freezing at all times.

8.6.1.2 rFVIII (Recombinant Factor VIII, octocog alfa /ADVATE)

ADVATE (rFVIII, octocog alfa) will be packaged in boxes with 2 glass vials, one containing the lyophilized rFVIII, and the second vial containing the diluent. Further details are provided in the IB and Pharmacy Manual. The ADVATE label will include, at a minimum, the actual FVIII:C potency and the date of expiration.

ADVATE (rFVIII, octocog alfa) should be refrigerated (2-8°C [36-46°F]) in powder form and should not be used beyond the expiration date printed on the vial.
Deviations from the storage condition have to be communicated and followed up with the sponsor. Inadequately stored product will have to be placed in quarantine and may only be used after written IP administration authorization by the sponsor. After removal of the product from the refrigerator the product must not be returned to the refrigerator and has to be used immediately. Avoid freezing at all times.

8.6.2 Reconstitution

The reconstitution procedures for both rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) products are detailed in the Pharmacy Manual.

8.6.3 Administration

Following reconstitution, rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) (in case of bleeding episode treatment) should be administered to study subjects at room temperature and within 3 hours of reconstitution. The reconstituted rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa), should be inspected for particulate matter and discoloration prior to administration, whenever the solution and container permit. The solution should be clear and colorless in appearance. If not, do not administer the product. Plastic syringes provided by the sponsor must be used since coagulation factors tend to stick to the surface of glass syringes.

Investigational product infusions should be given at a slow enough rate to ensure the subject's comfort. The rate should not exceed 4 mL/minute The investigator/ subject shall ensure that no visible residual volume remains in the syringe(s) and that the complete content is administered. Upon completion of the infusion, the butterfly catheter should be flushed with at least 2 mL of saline solution. In case of a (central) venous access device, the flush should be with at least 10 mL of saline solution. The IP infusions should be administered over a duration of 2 to 20 minutes, depending on the volume.

Only the actual potencies of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) as stated on the vial labels and described in the Pharmacy Manual should be used.

A variation of up to 10% of the intended dose for prophylactic infusions and of the intended dose for treatment of bleeding episodes is permissible and the exact dose should be recorded on the Case Report Form (CRF). Using of partial vials is not allowed.

At study visits where recovery analysis is being done, vials with the same lot numbers should be used throughout the PK IP infusion per subject.

For treatment of bleeding episodes, sequential administration will be done: separate syringes of the appropriate dose of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) will be prepared for sequential infusion. rVWF (vonicog alfa) should be infused first sequentially followed preferably within 10 minutes by infusion of ADVATE (rFVIII, octocog alfa). Only the actual potencies of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) as stated on the vial labels and described in the Pharmacy Manual should be used.

The final dose of rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) should be at a ratio of 1.3:1 ± 0.2.

8.6.4 Description of Treatment

8.6.4.1 PK-Assessment Treatment

For on-demand subjects, two PK assessments will be performed: an initial PK assessment after a wash-out period and a steady state PK assessments at the end of the study. The IP infusion for the initial PK assessment is scheduled on the baseline visit, which should be within 42 days after the completion of screening procedures and confirmation of eligibility. At the baseline visit the subjects will receive a dose of 50 ± 5 IU/kg rVWF:RCo for PK assessment. 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). A washout period of at least 5 days is required prior to infusion of rVWF (vonicog alpha) for PK assessment. The 2nd PK assessment for on-demand subjects will be performed at steady state at the end of the study(see Section 11.6). Subjects previously enrolled in rVWF studies **070701**, **071001** or **071101** and having previously undergone PK assessments in these studies are required to repeat the PK assessment due to different dose and time points used in these former studies.

For pdVWF switch subjects, two steady state PK assessments will be performed. The 1st PK will be assessed shortly after reaching steady state, which is expected to be 11 days after the 1st prophylactic dose for majority of the subjects, around the prophylactic dose #5-6. The 2nd PK will be at the end of the study. For steady state PK, 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) as long as it won't interfere with subject's the normal dosing schedule, otherwise the 96 hr sampling can be omitted (see Section 11.6). Final sample for PK analysis should be taken before next dose is administered.

8.6.4.2 Prophylaxis Initiation Treatment

The rVWF (vonicog alfa) prophylaxis initiation treatment visit will coincide with the 96 ± 2 h initial PK assessment for on-demand subjects. For pdVWF switch subjects, the rVWF (vonicog alfa) prophylaxis initiation treatment visit should occur within 42 days after the completion of screening procedures and confirmation of eligibility. At this visit subjects will receive their prophylaxis initiation dose. The prophylaxis doses are described in Section 8.6.4.3.

The subject will be trained on IP reconstitution and administration and may then qualify for home treatment (see Section 8.6.4.3.2). Refer toTable 6 (a/b) for study procedures and Table 8(a/b) for clinical laboratory assessments.

8.6.4.3 Prophylaxis Treatment

For on-demand subjects, the standard prophylactic dose is 50 ± 10 IU/kg rVWF:RCo, which may be increased up to 80 IU/kg. All on-demand subjects will initially receive rVWF (vonicog alfa) twice per week (Table 1, Schedule A). Examples of all dosing schedules are provided in Table 1.

For pdVWF switch subjects, the weekly dose (IU/kg) of IP for each patient 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 (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 (Table 1, Schedule B). A once weekly dose regimen will be allowed after switch to rVWF (vonicog alfa) only if the patient has been on a once weekly dose regimen with pdVWF.

Table 1
rVWF (vonicog alfa) Dosing Schedule Examples: Schedules A and B

Example	M	T	W	Th	F	Sat	Sun	M	T	W	Th	F	Sat	Sun
Schedule A	X				X			X				X		
Schedule B	X		X			X		X		X			X	

The prophylaxis dose may be further individualized within the range based on:

- available historical PK data
- type and severity of bleeding episodes the subject has experienced in the past and
- monitoring of appropriate clinical and laboratory measures

The individualized prophylaxic dose assignment will have to be agreed with the sponsor in advance, and the rationale should be well documented.

8.6.4.3.1 Adjustment of Dose or Dose Interval

In general, the dose and/or dose interval for each subject should not be changed unless prompted by clear medical needs. Dose and frequency adjustments should be agreed with the sponsor in advance unless it constitutes an urgent safety measure. The rationale for dosing adjustments needs to be documented in the subject's medical record.

For both OD and switch patients, dose escalations (not exceeding the upper dose limit of 80 IU/kg rVWF:RCo) and increase of dose frequency will only be allowed in case of insufficient therapeutic response with breakthrough bleeding episodes. The criteria for dose and/or frequency escalation are specific to each bleeding indication but, overall, involve 1 significant breakthrough bleeding episode despite the subject being compliant with scheduled prophylaxis treatment. For switch patients who require a dose escalation due to a breakthrough bleed, the frequency should be kept the same but the dose (IU VWF:RCo per infusion) should be increased up to 80 IU VWF:RCo. Following that, increases in frequency may be considered upon consultation with the Sponsor. For on demand subjects who require a dose escalation, at the discretion of the PI upon consultation with the Sponsor, the frequency may be kept the same but the dose (IU VWF:RCo per infusion) should be increased up to 80 IU VWF:RCo. If this proves to be insufficient, then the dosing frequency may be increased in these subjects. Table 2 presents the criteria for dosing escalation per each bleeding indication taken 50 ± 10 IU VWF:RCo/kg twice weekly dose as an example of subject's assigned starting dose.

The criteria are applicable for both OD and switch subjects who were initially assigned to twice weekly dosing. Subjects entering the study will begin prophylaxis treatment according to Schedule A (Table 1) and will remain at this dose and frequency until meeting the criteria for escalation to the next higher schedule: for example, from 2 infusions of 50 ± 10 IU VWF:RCo/kg/week to 3 infusions of 50 ± 10 IU VWF:RCo/kg/week (Schedule B) to achieve an adequate therapeutic response. If a subject started with a weekly dose (possible for switch subjects), similar criteria would apply except that the subject will be excalated to twice weekly dosing if frequency change is necessary.

Table 2
Criteria for Escalation Specific to Each Bleeding Indication

	Schedule A	Schedule B
Joint bleeding	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a spontaneous joint bleeding episode occurs while on this regimen, the subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B following its resolution	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
GI bleeding	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a severe GI bleeding episode, i.e., requiring red blood cell transfusion, occurs while on this regimen, the subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B following its resolution	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Menorrhagia	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) on days 1 and 2 of menses for 2 cycles. Menstrual flow will be monitored by the PBAC score. If the average pictorial chart score is > 185, then the subject will escalate to up to 80 IU/kg or, if necessary, to Schedule B	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) on days 1, 2, and 3 of menses. Menstrual flow will be monitored by the PBAC score.
Epistaxis	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. The subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B in the event of 1 occurrence of breakthrough bleeding requiring intervention such as iron replacement therapy, transfusion, packing, hospitalization; or 2 bleeding events that require treatment with factor replacement	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Oral and Other Mucosa	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. The subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B in the event of 1 occurrence of breakthrough bleeding requiring intervention such as iron replacement therapy, transfusion, packing, hospitalization; or 2 bleeding events that require treatment with factor replacement.	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Muscle and Soft Tissue	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a spontaneous bleeding episode occurs while on this schedule, the subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B following its resolution.	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.

Abbreviations: GI: gastrointestinal; PBAC: Pictorial Blood Assessment Chart.

If a subject does not adequately respond to rVWF (vonicog alfa) therapy, he/she will be evaluated for the presence of neutralizing and total binding anti-VWF antibodies (see Section 12.9.3.2).

If a subject experiences a bleed while receiving rVWF (vonicog alfa) three times per week, the investigator should treat the bleed with rVWF (vonicog alfa) at doses up to 80 IU VWF:RCo/kg at a frequency determined by the investigator until the bleed resolves. Upon resolution of the bleeding event, the subject will return to their assigned prophylaxis regimen.

It is essential for the success of this study that the subjects adhere to treatment regimens. Therefore, procedures for monitoring subject's compliance are implemented (see Section 10.7).

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. For example, a subject routinely infuses IP on Monday and Thursday, he/she misses the Monday time point and therefore may infuse the IP on the next day (Tuesday) and thereafter proceed with infusing the IP on Thursday (considering a minimum 12 hours between the infusions) and return to the initial schedule.

If more than 30% of infusions of IP are missed within the visit interval of 3 months the subject will be discontinued from the study (see Section 9.4).

8.6.4.3.2 General Instructions for Home Treatment for Prophylaxis

At the discretion of the investigator, a subject may be considered suitable for home treatment only after the subject has received at least 1 infusion of IP in the clinic, either during planned prophylactic IP exposure or during the treatment of bleeding episodes, and meets the following additional criteria:

1. Fully understands the concept of a clinical study and related documentation (documented training of at least 30 minutes),
2. Has a history of previous experience with home treatment including self-administration and treatment with VWF containing concentrates,
3. Has adequate time for initial training of the study drug preparation (preparation, mixing and infusion of the IP(s) (documented training of at least 30 minutes).

This applies both to subjects who were on prior on-demand treatment and to subjects switching form prophylaxis with pdVWF. In the event a healthcare professional is required to administer IP, he/she must be trained and qualified by the investigator on the above procedures prior to the decision for home treatment. A Subject Guideline detailing all instructions and information listed above will be provided to each subject.

8.6.4.4 Treatment of Bleeding Episodes

8.6.4.4.1 General Instructions for Home Treatment of Bleeding Episodes

If a subject experiences a bleeding episode, he/she should contact the study site immediately and the site investigator should provide instructions on the treatment regimen. If the subject initiates the treatment at home, he/she should at least follow up with the study site if a visit is needed as per the standard of care at the center.

In the event a healthcare professional is required to administer treatment at the subject's home, he/she must be trained and qualified by the site investigator on the above procedures prior to the decision for home treatment. Once a subject has received 1 infusion of rVWF (vonicog alfa) in the clinic (either during planned IP exposure or during the treatment of a bleeding episode) and meets the criteria for home treatment, the treatment of bleeding episodes with IP can be conducted at home (see Section 8.6.4.3.2).

If a subject is not qualified for home treatment, rVWF (vonicog alfa) infusions must be administered at the study site.

If a subject experiences a bleeding episode that requires treatment between the screening and the prophylaxis initiation visit, the subject will be treated with IP (rVWF with or without ADVATE). Treatment with IP must occur at the study site unless the subject has previously qualified for home treatment with rVWF (vonicog alfa). If rVWF (vonicog alfa) treatment is not feasible, the subject may use his/her standard of care, such as commercial pdVWF/FVIII products. In any case a washout period of at least 5 days is required prior to rVWF (vonicog alfa) PK infusion at the initial PK assessment visit for on-demand subjects.

If a subject experiences a bleeding episode requiring treatment during the PK assessment, rVWF (vonicog alfa) should be used to treat the bleed. Blood draws for PK assessment will be stopped and the PK assessments will be repeated once the bleed has resolved and the subject is free of any symptoms related with the bleeding episode. Dose and frequency of rVWF (vonicog alfa) infusions or any other replacement therapy to stop the bleed should be recorded in the electronic Case Report Form (eCRF), and the reason for the use of any non-IP product or therapy should be documented.

8.6.4.4.2 Dosing Recommendations for Treatment of Bleeding Episodes

If an acute bleeding episode occurs, the subject will be treated with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa). It is the sponsor's opinion that, in many cases, treatment with ADVATE (rFVIII, octocog alfa) may not be necessary, since rVWF (vonicog alfa) prophylaxis will serve to increase endogenous FVIII levels. However, if endogenous FVIII is below 30-40 % or is unknown and cannot be estimated from the subject's PK study, an infusion of rVWF: ADVATE at an rVWF: ADVATE ratio of 1.3:1± 0.2 should be administered initially. Subsequent infusions should be with rVWF:RCo 40 to 60 IU/kg with or, in many cases,without 30 to 45 IU/kg ADVATE (only to be administered if plasma FVIII levels fall below 30 IU/L during the treatment period). Dosing may be adjusted downward or upward up to 80 IU/kg rVWF at the treating physician's discretion based upon the subject's prior history, PK and other factors.

If FVIII levels are not available, dosing is at the discretion of the investigator based upon the individual subject's PK data. Using ADVATE (rFVIII, octocog alfa) in addition to rVWF (vonicog alfa) in subsequent doses carries the risk of an excessive rise in FVIII:C. Therefore, reduced doses of ADVATE (rFVIII, octocog alfa) and/or prolongation of the dose interval should be considered.

The following is general guidance and the sponsor's suggestion for treatment of breakthrough bleeds, however each PI will determine the treatment based on the local acceptable practice how to monitor and adjust treatment for a bleeding episode. An effort should be made to discuss with the sponsor (or sponsor's delegate) the treatment strategy.

In general the aim of the initial dose should be full replacement of VWF with VWF:RCo levels of >0.6 IU/ml (60%) and FVIII:C of >0.4 IU/mL (40%). In major bleeding episodes, subsequent doses should keep the trough level of VWF:RCo >50% for 3 days and then as deemed necessary by the investigator for subsequent days. In moderate bleeding episodes, the dose and trough level may be reduced to >30% for as long as deemed necessary by the investigator. Treatment for minor bleeding episodes will generally consist of only 1 or 2 doses of rVWF (vonicog alfa) IP.

If the VWF:RCo level is above 150%, a planned treatment should be delayed by at least 12 hours; if the VWF:RCo level is above 200%, a planned treatment should be delayed by at least 24 hours. In either case, a lower subsequent dose (e.g., 20 IU/kg VWF:RCo) may be appropriate.

Dosing recommendations are listed in Table 3.

Dosage must be individualized based on the subject's weight, VWD type, and the severity of the bleeding episode, as well as on monitoring of appropriate clinical and laboratory measures. In the phase 1 study **070701**, 1.0 IU/kg VWF:RCo raised the circulating level of VWF:RCo by 0.017 IU/mL (1.7 %). In the same study, the observed mean half-life for rVWF (vonicog alfa) was 19.3 hours, with a standard deviation of 10.9 hours.

Table 3
rVWF:RCo Dosing Recommendations for the Treatment of Bleeding Episodes Due to VWD

Classification of VWD	Hemorrhage	Dosage (IU VWF:RCo/kg BW)
Type 1 • Severe (Baseline VWF:RCo activity typically <20%)	Minor (e.g., epistaxis, oral bleeding, menorrhagia[a])	40 to 50 IU/kg (1 or 2 doses)
	Major (e.g., severe or refractory epistaxis, menorrhagia*, GI bleeding, CNS trauma, hemarthrosis, or traumatic hemorrhage)	Initial dose 50 to 75 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment
Type 2 (all variants) and Type 3	Minor (clinical indications above)	40 to 50 IU/kg (1 or 2 doses)
	Major (clinical indications above)	Initial dose of 60 to 80 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment

[a] Menorrhagia is defined as excessive bleeding during menstruation. A diagnosis of menorrhagia will be defined by a prospectively completed Pictorial Blood Assessment Chart (PBAC) score >185 and normal cervical cytology or requiring use of a VWF-containing concentrate for treatment of excessive menstrual bleeding for at least one menstrual cycle during the prior year.

Variances of up to 10% in dosing are permissible during treatment of bleeding episodes, but rounding to the nearest vial size should be avoided.

Subjects with non-neutralizing binding anti-VWF antibodies should initially be treated with a dose known to be efficacious based on the subject's medical treatment history which may differ from the recommendations provided in Table 3. Subjects should be monitored for lack of efficacy as well as for FVIII (mandatory), VWF:RCo (mandatory), and VWF:Ag (optional where testing is not available) levels after 3 to 6 hours. Re-dosing with rVWF (vonicog alfa) in combination with ADVATE (rFVIII, octocog alfa) using the same (initial) dose and adaptation of the dosing frequency should be considered until cessation of the bleed, if the FVIII and/or VWF:RCo levels drop below 30%-50% depending on bleeding severity.

The number of subsequent infusions and the dosage levels prescribed will be determined by the investigator on the basis of the clinical severity, response to current therapy, available laboratory data, and the subject's historical treatment for similar bleeding episodes.

8.6.4.5 Treatment of Surgical Bleeding

Subjects enrolled in this study who require surgery or dental procedures will be treated with IP to manage their surgical bleeding then afterwards will resume their prophylactic rVWF (vonicog alfa) treatment schedule. Subjects who at time of screening have an already scheduled surgical intervention are not eligible for participation in the study.

8.6.4.5.1 Major, Minor and Oral Surgery Definition

The following definitions and criteria are used to serve as a guidance for *major, minor and oral surgery*.

Major surgeries generally refer to major orthopedic surgery (e.g., joint replacement, arthroscopic or open synovectomy, arthrodesis, hardware removals like plates or intramedullary nails, etc.), major abdominal surgery (e.g. open or laparoscopic hernioplasty, cholecystectomy, colon or small bowel resection, etc.), major gynecological surgery (e.g. open or laparoscopic myomectomy, hysterectomy, removal of endometriosis, polyps, cysts, adhesiolysis, etc.), major head and neck surgery (e.g.: tonsillectomy, adenoidectomy, rhinoplasty, lymphadenectomy, thyroidectomy, parotidectomy. etc.), any intracranial , cardiovascular or spinal surgery and any other surgery which has a significant risk of large volume blood loss or blood loss into a confined anatomical space. Extraction of impacted third molars is generally also considered major surgery due to the expected difficulty of surgery and the expected blood loss.

Minor surgeries generally refer to interventions such as placement of intravenous access devices, removal of small skin lesions, arthroscopy, gastroscopy, colonoscopy or conisation.

Oral surgeries comprise extractions of fewer than three teeth, if the teeth are non-molars and have no bony involvement.

A summary schedule of visit assessments and laboratory sampling is included in Supplement tables in Section 20.2.1 and Section 20.3.1.

8.6.4.5.2 Preoperative Priming Dose

12- 24 hours prior to surgery, a priming dose with rVWF (vonicog alfa), using the rVWF IR and $T_{1/2}$ for this subject , will be infused to allow the endogenous FVIII levels to raise to at least 30 IU/dL (minor, oral surgery), or 60 IU/dL (major surgery) at the time of the loading dose of rVWF (vonicog alfa) is infused.

As a general guidance a priming dose of 40-60 IU/kg rVWF:RCo will be administered. If not assessed prior to the preoperative priming dose, a IR recovery may be calculated for subjects undergoing minor and oral surgery.

8.6.4.5.3 Preoperative Loading Dose

An rVWF (vonicog alfa) loading dose should be administed within 3 hours before surgery. VWF and FVIII levels should be assessed within 3 hours prior to surgery initiation and results must be available prior to administering the loading dose. If FVIII levels prior to loading dose administration are not at least 30 IU/dL (minor, oral surgery), or 60 IU/dL (major surgery) ADVATE (rFVIII, octocog alfa) will be administered in addition to rVWF (vonicog alfa) in order to raise FVIII:C levels to recommended levels.

The preoperative loading dose will be calculated as the difference in the target peak and baseline plasma VWF:RCo levels divided by the IR (ΔVWF:RCo x BW (kg) /IR). The PK results will be provided prior to the planned surgery. If the IR is not available, assume an IR of 1.7 IU/dL per IU/kg and calculate the initial dose as follows: (100 − baseline plasma VWF:RCo) x BW (kg) / 1.7. For minor and oral surgery, the IR from the Preoperative Priming Dose visit will be used to guide dosing and the target peak is 50-60 IU/dL VWF:RCo and 40-50 IU/dL FVIII. For major surgery, the target peak is 100IU/dL VWF:RCo and 80-100 IU/dL FVIII.

The surgery may only start after normalization of the activated partial thromboplastin time (aPTT).

8.6.4.5.4 Intra- and Postoperative (maintenance) Dosing

After the preoperative loading dose(s), subjects who have not achieved the desired postinfusion recovery will continue to receive rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) as a bolus infusion, depending on VWF and FVIII levels. The peri- and post-operative substitution regimen will be individualized according to the PK results, intensity and duration of the hemostatic challenge, and the institution's standard of care.

Subjects undergoing minor surgery will be infused with rVWF (vonicog alfa) every 12-24 hours or every other day, targerting ≥30IU/dL (rVWF and FVIII) for at least the first 48 hours.

Subjects undergoing oral surgery will be infused with rVWF (vonicog alfa) at least once within the first 8-12 hours, targeting ≥30 IU/dL (rVWF and FVIII).

Subjects undergoing major surgery will be infused with rVWF (vonicog alfa) every 12-24 hours for at least the first 72 hours post-surgery, targeting a VWF:RCo and FVIII:C trough plasma level >50 IU/dL, followed by further treatment post-72 hours for as long as deemed necessary by the Investigator, targeting a VWF:RCo and FVIII:C trough plasma level of ≥30 IU/dL.

Dose modifications based on pre-infusion VWF/FVIII levels will be performed as needed. For subsequent infusions post surgery, in case pre-infusion levels are not available prior to the consecutive infusion in a timely manner, pre-infusion levels from the previous dose may be used by the investigator for dosing guidance.

Peak plasma level guidance is matching to Section 8.6.4.4.2

A schedule of all perioperative visit assessments and laboratory sampling can be found in supplement tables in Section 20.2.1 and Section 20.3.1.

8.6.4.6 Thrombosis Prophylaxis

Thromboembolic events have been reported in patients who have VWD, especially in the setting of known risk factors for thrombosis including low ADAMTS13 levels. Therefore, subjects who are at risk for developing thromboembolic events should be monitored for early signs of thrombosis, and prophylaxis measures against thromboembolism should be instituted according to current recommendations and standard of care. For all subjects who are VWD patients and are receiving VWF concentrate, attention should be given to avoid exceeding maximal recommended plasma activity levels of VWF:RCo (250 IU/dL) and FVIII (250 IU/dL).

Anticoagulation measures, such as heparin, are acceptable and should follow study site standards. The investigator will record the use and reasons for such measures/agents on the appropriate CRF.

8.6.5 Investigational Product Accountability

The investigator will ensure that the IP(s) is stored as specified in the Pharmacy Manual and that the storage area is secured, with access limited to authorized study personnel. All temperature excursions at the subject's home need to be monitored by the site (please refer to the pharmacy manual). The investigator will maintain records that the IP(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. The IP(s) must be dispensed only at the study site or other suitable location (e.g., infusion center; home, as applicable per study design), as specified in the protocol (see Section 10). Records will be maintained that includes the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

8.7 Source Data

Per ICH E6(R2) on GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). These may be in paper and/or electronic format. Source documents for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

No data will be entered directly onto the CRF.

For additional information on study documentation and CRFs refer to Section 17.2. The use of subject diaries is described in Section 10.5.

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding
   a. Type 1 (VWF:RCo <20 IU/dL) or,
   b. Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2M or,
   c. Type 3 (VWF:Ag ≤3 IU/dL).
2. Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.
3. For on-demand patient group, subject currently receiving on-demand treatment for whom prophylactic treatment is recommended by the investigator.
4. For pdVWF switch patient group, subject has been receiving prophylactic treatmentof pdVWF products for no less than 12 months prior to screening.
5. For on-demand patient group, subject has ≥3 documented spontaneous bleeds (not including menorrhagia) requiring VWF treatment during the past 12 months.
6. Availability of records to reliably evaluate type, frequency and treatment of bleeding episodes during at least 12 months preceding enrollment. Up to 24 months retrospective data should be collected if available. Availability of dosing and factor consumption during 12 months (up to 24 months) of treatment prior to enrollment is required for pdVWF switch subjects and is desired (but not a requirement) for on-demand subjects.
7. Subject is ≥18 years old at the time of screening and has a body mass index ≥15 but <40 kg/m^2.
8. If female of childbearing potential, subject presents with a negative blood/urine pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.[i]
9. Subject is willing and able to comply with the requirements of the protocol.

[i] Refer to Section 20.4 for a list of adequate contraceptive methods for females of childbearing potential.

9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

1. The subject has been diagnosed with Type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD (eg qualitative and quantitative platelet disorders or prothrombin time (PT)/international normalized ratio [INR] >1.4).
2. The subject is currently receiving prophylactic treatment with more than 5 infusions per week.
3. The subject is currently receiving prophylactic treatment with a weekly dose exceeding 240 IU/kg.
4. The subject has a history or presence of a VWF inhibitor at screening.
5. The subject has a history or presence of a FVIII inhibitor with a titer ≥0.4 Bethesda units (BU) (by Nijmegen modified Bethesda assay) or ≥0.6 BU (by Bethesda assay).
6. The subject has a known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins.
7. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
8. The subject has a medical history of a thromboembolic event.
9. The subject is human immunodeficiency virus (HIV) positive with an absolute Helper T cell (CD4) count <200/mm^3.
10. The subject has been diagnosed with significant liver disease per investigator's medical assessment of the subject's current condition or medical history or as evidenced by any of the following: serum alanine aminotransferase (ALT) greater than 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).
11. The subject has been diagnosed with renal disease, with a serum creatinine (CR) level ≥2.5 mg/dL.
12. The subject has a platelet count <100,000/mL at screening.
13. The subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to signing the informed consent.

14. The subject is pregnant or lactating at the time of enrollment.
15. Patient has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
16. The subject has participated in another clinical study involving another IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
17. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
18. The subject is scheduled for a surgical intervention.
19. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
20. The subject has a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
21. The subject is in prison or compulsory detention by regulatory and/or juridical order.
22. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.

9.3 Delay Criteria

1. If the subject has an acute bleeding episode or presents with an acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) the screening visit will be postponed until the subject has recovered.

9.4 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (i.e., reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the termination visit (including cases of withdrawal or discontinuation) are described in Section 10.6 and Section 20.2.

Discontinuation (i.e., complete withdrawal from study participation) may be due to dropout (i.e., active discontinuation by subject) or loss to follow-up (i.e., discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also will be withdrawn from treatment or discontinued from further study participation for the following reasons:

1. The subject is scheduled for an extended treatment period >3 months with non-topical immunomodulating drugs other than anti-retroviral chemotherapy (e.g., α-interferon, corticosteroid agents [equivalent to hydrocortisone greater than 10 mg/day]) during the course of the study.
2. Subjects with chronic hepatitis B or C develop ALT/AST levels exceeding 5 times the ULN for >1 month.
3. Subjects who experience severe hypersensitivity reactions, e.g., anaphylaxis upon exposure to rVWF (vonicog alfa).
4. Subjects who develop a neutralizing inhibitor to rVWF (vonicog alfa) and/or ADVATE (rFVIII, octocog alfa) (biological assays) that results in significant clinical effect, including but not limited to increasing the weekly dose of rVWF by $\geq$ 50%.
5. Subjects who demonstrate clinical signs of thromboembolic events.
6. The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through completion of the pregnancy and up to 1 year post delivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome.
7. The subject begins lactating. IP exposure will be discontinued. The investigator will record a narrative description of the course of the baby's development.
8. The subject is not compliant with the prophylactic treatment regimen and does not adhere to the frequency of IP administration. Once >30% of infusions are missed within a visit interval (3 months), the subject will be discontinued from further participation in the study.
9. The subject repeatedly uses other VWF products for prophylaxis or for the treatment of bleeding episodes in the absence of an acceptable justification to the sponsor.

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient who provides informed consent (i.e., signs and dates the informed consent form) is considered a subject enrolled in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (e.g., 071301) to be provided by the sponsor, 2- or 3-digit number study site number (e.g., 02) to be provided by the sponsor, and 3- or 4-digit subject number (e.g., 0003) reflecting the order of enrollment (i.e., signing the informed consent form). For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 071301-020003. All study documents (e.g., CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The study site is responsible for maintaining a screening log that includes all subjects who provided informed consent. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRF, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

The overall study design is illustrated in the Figure 1. Details on the procedures to be performed at each study visit, including screening, are provided in Supplement 20.2 „Schedule of Study Procedures and Assessments“ and Supplement 20.3 „Clinical Laboratory Assessments“.

10.3.1 Screening Visit

Written informed consent must be obtained from each subject before any study related procedures are performed. To initiate screening procedures, at least 72 hours must have elapsed since the last VWF administration for on-demand subjects and the subject must not be actively bleeding at the time of screening. For switch subjects, the usual interval between their pdVWF prophy infusions must have elapsed since the last VWF administration and the subject must not be actively bleeding at the time of screening. Multimer analysis and VWD gene mutation analysis should be performed at screening if not available in the subject's medical history.

The screening visit will be delayed if the subjects presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like symptoms, inflammatory diseases) until the event has resolved. All screening procedures and confirmation of eligibility shall take place within 42 days prior to the first infusion of IP. If the IP is not infused within 42 days, all screening assessments except blood group, human leukocyte antigen (HLA), genetics, multimeric pattern and [redacted], must be repeated to reconfirm eligibility. Refer to Supplement 20.2 and Supplement 20.3. Upon completion of screening procedures, subject eligibility will be confirmed by the sponsor on a subject eligibility form before additional study procedures are undertaken. The subject will maintain a diary that will include infusion logs (see Section 10.5). The allocation of IP will be initiated after the subject has qualified for home treatment (see Section 8.6.4.3.2).

In the event of a subject experiencing a bleeding episode that requires treatment between the screening visit and the subsequent visit (i.e. initial PK assessment visit for on-demand subjects or prophylaxis initiation visit for switch subjects), the subject will be treated with rVWF (vonicog alfa). If rVWF (vonicog alfa) is not available for any reason, e.g., subject not yet trained on IP administration, study site visit for IP administration not feasible, etc., the subject may use his/her standard of care, such as commercial pdVWF/FVIII products, and the reason for the use of non-IP products should be clearly documented.

10.3.2 Baseline Visit – Initial PK Assessment (On-demand Subjects Only)

After screening and confirmation of eligibility on-demand subjects will undergo an initial PK assessment. Subjects will receive a dose of 50 ± 5 IU/kg rVWF:RCo to determine VWF and FVIII levels. 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). See Section 20.2 and Section 20.3. IP infusion vials from the same lot number should be used for all PK-assessments per subject. Samples for measurement of FVIII and VWF activity taken through to 6 hours post-infusion will be obtained from an extremity different from that used for the infusion of IP. Where needed, the phlebotomy site will be kept patent via an infusion of normal saline. In this event, at least 5 mL of blood will be collected and discarded before collection of the next test sample into a fresh syringe.

If the subject has a central venous catheter, the central line should be used to administer the infusion and a peripheral venipuncture should be used to collect the blood samples.

In the event that a blood sample must be drawn through the central line used for administration of IP, the line must first be flushed with at least 10 mL normal saline or other suitable catheter flush solution that does not contain anticoagulant. At least 5 mL of whole blood must be collected and discarded prior to obtaining the sample.

If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.6.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment.

For pdVWF switch subjects, PK profile will not be assessed until reaching steady state after initiation of prophylaxis (see Section 10.3.4).

10.3.3 Prophylaxis Initiation Visit

The prophylaxis initiation visit will occur after the blood sample for the 96 hour PK assessment is drawn for on-demand subjects or within 42 days after screening and confirmation of eligibility for pdVWF switch subjects. The subject will receive the first rVWF (vonicog alfa) prophylactic dose of rVWF: RCo. Details on dose are provided in Section 8.6.4.3.

Procedures and assessments at this visit include (but are not limited to): AEs, bleeding episodes, medications taken, and non-drug therapies. Within 2 hours prior the IP infusion, a physical examination will be performed. Vital signs will be assessed within 30 minutes prior to IP rVWF (vonicog alfa) infusion and 30 minutes ± 15 minutes after IP infusion. Further details are provided in Supplement 20.2 and Supplement 20.3.

10.3.4 Initial Steady State PK-Assessment (pdVWF switch subjects only)

For pdVWF switch subjects, a full PK profile will be assessed at steady state conditions on two occasions. The initial PK assessment will be performed shortly after reaching steady state after starting prophylaxis dosing, which is suggested after 11 days post the 1st, around prophylaxis dose #5-6. The 2nd PK assessment at steady state will be performed at the end of the study.

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). In case the dosing schedule does not permit the 96 hr sampling, this sampling time point can be omitted (See Section 11.6). IP infusion vials from the same lot number should be used for all PK-assessments per subject.

Samples for measurement of FVIII and VWF activity taken through to 6 hours post-infusion will be obtained from an extremity different from that used for the infusion of IP. Where needed, the phlebotomy site will be kept patent via an infusion of normal saline. In this event, at least 5 mL of blood will be collected and discarded before collection of the next test sample into a fresh syringe.

If the subject has a central venous catheter, the central line should be used to administer the infusion and a peripheral venipuncture should be used to collect the blood samples. In the event that a blood sample must be drawn through the central line used for administration of IP, the line must first be flushed with at least 10 mL normal saline or other suitable catheter flush solution that does not contain anticoagulant. At least 5 mL of whole blood must be collected and discarded prior to obtaining the sample.

If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.6.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment. In case of surgery or bleeding, the PK assessment should be performed after 11 days after 1st prophylactic dose after re-start of prophylactic regimen. See section 11.6 for more details.

10.3.5 Treatment of Bleeding Episodes

Treatment of bleeding episodes is described in detail in Section 8.6.4.4 and treatment of perioperative bleeding is described in detail in Section 8.6.4.5.

10.3.6 Perioperative Visits (only applicable if surgery is needed)

The perioperative visits from priming dose through postoperative day 14 will be required to check daily intra- and postoperative weight-adjusted dose of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa). Details on the procedures and assessments performed at each visit can be found in supplement tables in Section 20.2.1 and Section 20.3.1.

10.3.7 Follow-Up Visits

Visits will be performed after the prophylaxis initiation visit at 1 month ± 1 week, 2 months ± 1 week, and 3 months ± 2 weeks and thereafter every three months ± 2 weeks. Additional visits may occur if clinically indicated (see Section 10.3.8).

When possible, site visits should be scheduled on days when the subject is expected to infuse rVWF (vonicog alfa). Within 2 hours prior to the rVWF (vonicog alfa) IP infusion, a physical examination will be performed. Vital signs will be assessed within 30 minutes prior to IP infusion and 30 minutes ± 15 minutes after IP infusion. Incremental recovery (IR) will be determined at each follow-up visit based on VWF:RCo activity assessed prior to and after IP infusion.

The blood sample for IR analysis will be drawn within 30 minutes prior to IP infusion and 30 minutes ± 5 minutes after IP infusion. rVWF (vonicog alfa) will be infused at the regular prophylactic dose. For each subject's recovery analysis IP infusion, vials from the same lot number should be used.

Testing for VWF:RCo VWF:CB, rVWF:Ag, and FVIII:C level will be performed using the blood sample obtained before and after IP infusion.

The blood sample prior to IP infusion will also be used for the assessment of neutralizing and binding antibodies, clinical chemistry and hematology. For on-demand subjects, a washout period of at least 72 hours after the last infusion applies before the blood draw for the immunogenicity assays. For switch subjects, the wash out period may be reduced to the time interval between their pdVWF prophy infusions Bleeding episodes and the hemostatic efficacy will be evaluated based on the review of the patient diary. See Section 20.2 and Section 20.3. The evaluation of IP consumption and treatment compliance will be performed based on subject's diary entries. If a subject is not compliant with the prophylactic treatment regimen and does not adhere to the required frequency of administration of IP infusions (>30% of infusions were missed within a visit interval [3 months]) the subject will be withdrawn from the study.

At the 6 months ± 2 week visit an ECG will be performed and [redacted] data will be collected.

For the hemostatic efficacy assessment the following information will be recorded by the subject in the patient diary: bleeding location, type, severity, onset and resolution date and time, infusion date and time, clinical efficacy according to the rating scale. If at any time during the study a subject's bleeding episode does not adequately respond to rVWF (vonicog alfa) therapy, he/she will be evaluated for the presence of neutralizing and total binding antibodies. Refer to Section 12.9.3.2.

Further guidance on completing the subject's diary will be provided to the subjects during training for home treatment (see Section 8.6.4.3.2).

10.3.8 Unscheduled Visits

For any unscheduled visit (except for collection of IP) a clinical assessment will be performed as per the scheduled follow-up visits with the exception of [redacted], ECG, and IR determination (refer to Supplement 20.2 and Supplement 20.3).

Subjects who have more than one bleeding episode in 3 months, or an increased frequency of bleeding, should go to the study site for an unscheduled visit.

Follow-up visits after the subject has experienced a bleed may be requested by the investigator. Additional assessments may be required which are at the discretion of the investigator.

10.3.9 End of Study PK Assessment and Study Termination Visit

At the 12* month ± 2 week visit, a full PK analysis at steady state will be performed for both cohorts: on-demand and switch subjects. 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) unless dosing schedule does not permit, in which case the 96 hr sampling can be omitted. If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.6.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment and the PK assessment should be performed after 11 days after 1st prophylactic dose after re-start of prophylactic regimen. See section 11.6 for more details.

Refer to Supplement 20.2 and Supplement 20.3 for the other assessments to be performed at the PK assessment and study completion visits.

For on-demand subjects, a washout period of at least 72 hours is required between the PK infusion and the study termination visit (at the time of the 96 hour postinfusion PK assessment). For switch subjects, the wash out period may be reduced to the time interval between their rVWF (vonicog alfa) prophy infusions.Refer to Supplement 20.2 and Supplement 20.3 for the list of assessments to be performed at the termination visit.

Subjects will be offered the option to continue to receive rVWF (vonicog alfa) in a long-term continuation study*.

* Study treatment period is extended by 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. For subjects whose completion date is extended beyond the 12-month visit due to delay in continuation study start-up, the 12-month ± 2 weeks visit will be considered as a follow-up visit, and EOS visit will be performed once the subject can rollover into the continuation study, from 12 month ± 2 weeks to 15 month ± 2 weeks post prophylaxis initiation visit, as applicable. Both the 12-month ± 2 weeks visit rescheduled as a follow-up visit, and the rescheduled EOS visit will be recorded in the CRF.

10.4 Medications and Non-Drug Therapies

The following medications and non-drug therapies are **not** permitted within 30 days before study entry and during the course of the study:

Medications:

- 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) and an extended treatment period >3 months.
- Another investigational and/or interventional study drug (except rVWF and FVIII administered under the surgery protocol).

A subject who has taken any of these medications or received any of these non-drug therapies during the study will be withdrawn from the study.

The following medications are permitted during the course of the study:

- Antifibrinolytics (e.g., tranexamic acid, ε-amino caproic acid) or topical hemostats as needed, according to each institution's standard of care. These may be used, in accordance with local standard clinical practice, as the initial or only treatment for minor and moderate bleeding events. However, if the bleeding has not stopped within 24 hour following administration of this non-VWF treatment, infusion(s) with rVWF (vonicog alfa) should be started per protocol
- Emergent use of a VWF concentrate other than rVWF (vonicog alfa) may be permissible under certain circumstances (see Section 8.6.4.4.1)

Details of all adjunctive hemostatic medication used, including dose and reason for use, must be recorded in the eCRF.

10.5 Subject Diary

An electronic subject diary will be provided to each subject at the screening visit to record the following information:

1. IP infusions to include date, start and stop times of the infusion, number of vials utilized, and infusion volume for prophylactic treatment or treatment of spontaneous and traumatic bleeding episodes
2. Details of bleeding episodes (site, type, severity and date/time of bleeding) and response to treatment as described in Section 8.6.4.4
3. Subjective hemostatic efficacy assessments
4. Untoward events/unwanted experiences
5. Concomitant medications (including immunizations) and non-drug therapies
6. Patient Reported Outcomes (PROs)

Subjects and/or their legally authorized representatives will be trained on use of the diary. The diary will be provided in electronic format and remain with the subject for the duration of the study. The investigator will review the diary for completeness and request missing information periodically and in a timely manner. The investigator will record/capture any unwanted experience reported by the subject which may qualify as an AE on the AE eCRF.

Infusions performed at the study site will first be recorded in the site's source documents and not in the patient diary.

Subject entries in the diary will serve as source records. During study participation the investigator has access to the database holding the subject diary data. After study closure, the investigator will receive the diary records for their subjects, including audit trail records, in PDF format. The data will be transmitted to the CRF by a validated transfer.

Paper diary may be utilized in rare case where electronic diary use is not possible.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have completed all study procedures according with the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, AE (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, e.g., technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the study termination visit. If the termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the termination visit.
If a subject terminates participation in the study and does not return for termination visit, his/her last recorded assessments shall remain with the last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.2 Schedule of Study Procedures and Assessments and Supplement 20.3 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

10.7 Procedures for Monitoring Subject Compliance

Subject compliance with the procedures of this study (treatment regimens and study visits) will be monitored by the investigator or/a licensed healthcare professional at the study site.

During the regular scheduled follow-up visits a direct review of the subject's source data (e-diaries) will be performed at the sites and evaluated against the protocol requirements. In addition drug accountability will be evaluated at each follow-up study visit and the study termination visit by comparing the infusions recorded in the subject diary with empty vials returned by each subject to the study site, and the study site's dispensing record. Protocol deviations will be noted in the final report.

11. ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

11.1 Assessment of Spontaneous Bleeding Episodes/Annualized Bleed Rate

The annualized bleed rate (ABR) will be assessed based upon each individual spontaneous bleed, requiring coagulation factor replacement therapy, i.e., rVWF (vonicog alfa) treatment. The following details on bleeding episodes will be recorded by the subject in the electronic diary (for home treatment), the subject's healthcare provider in the site's source documents (for treatments away from the primary investigative site), or by authorized, qualified personnel at the participating site in the subject's medical records (for hospital-based treatment):

- Location of bleed; i.e., joint, menorrhagia, epistaxis, gastrointestinal, soft tissue, muscle, body cavity, intracranial, etc.
- Type of bleed; i.e., spontaneous, traumatic, unknown
- Severity of bleed; i.e., minor, moderate, and major (see Table 3)
- Date and time of onset of bleed
- Date and time of each infusion of rVWF (vonicog alfa) or rVWF (vonicog alfa)-ADVATE (rFVIII, octocog alfa) used to treat a bleeding episode
- Date and time of resolution of the bleeding episode

Study site personnel are qualified after they have undergone training during the qualification of the site.

All types of bleeds, including traumatic bleeds, will be recorded. Bleeding episodes should be organized by where they occur in addition to whether they occurred spontaneously or due to a traumatic event.

Bleeds occurring at the same anatomical location (e.g., right knee) with the same etiology (i.e., spontaneous versus injury) within 24 hours after onset of the first bleed will be considered a single bleed. Bleeding occurring at multiple locations related to the same injury (e.g., knee and ankle bleeds following a fall) will be counted as a single bleeding episode.

All efforts should be made to use rVWF (vonicog alfa) for treatment of bleeding episodes. If needed, the use of a VWF concentrate other than IP for the treatment of bleeding episodes will not disqualify the subject from further participation in the study.

11.2 Evaluation of ABR Before rVWF Prophylaxis and ABR Under rVWF Prophylactic Treatment

At screening, the subject's medical history will be recorded, including the number and location of all spontaneous and traumatic bleeding episodes within the past 12 months (up to 24 months if available). The maximum interval of bleed-free periods as well as trauma induced bleeding episodes will also be recorded (prospectively and retrospectively).

11.3 Number of Infusions and Total Weight Adjusted Consumption of rVWF and ADVATE and historical prophylaxis dosing and factor consumption during pdVWF prophylaxis treatment prior to enrollment

The number of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) (in case of bleeding episode treatment) infusions will be logged in the subject diary. Based on these entries the weight adjusted consumption will be calculated.

At the screening, historical pdVWF dosage and dosing frequency during 12 and up to 24 months of pdVWF prophylactic treatment prior to enrollment will be recorded for the pdVWF switch subjects in order to calculate the consumption of pdVWF.

11.4 Assessment of Efficacy for Treatment of Bleeding Episode

Investigators will be asked to assess and record hemostatic efficacy after resolution of each bleeding episode using the 4-scale rating system outlined in Table 4.

Table 4
Efficacy Rating Scale

Rating	Efficacy Rating Criterion	
	Minor and Moderate Bleeding Events	**Major Bleeding Events**
Excellent (=1)	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF containing coagulation factor containing product required	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF containing coagulation factor containing product required
Good (=2)	1-2 infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required	< 1.5 x infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required
Moderate (=3)	3 or more infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required	≥ 1.5 x infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required
None (=4)	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF containing coagulation factor containing product required	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF containing coagulation factor containing product required

11.5 Assessment of Efficacy for Treatment for Surgical Bleeding

For those undergoing surgery, the operating surgeon will be asked to assess and record actual versus predicated blood loss and intraoperative hemostatic efficacy immediately after surgery.

The investigator will be asked to assess and record an overall assessment of hemostatic efficacy 24 hours after the last perioperative rVWF (vonicog alfa) infusion or at day 14 post-operation, whichever occurs first, using the 4-scale rating system described in Table 5.

Table 5
Assessment of Hemostatic Efficacy

Rating	Overall Assessment of Hemostatic Efficacy 24 Hours After the Last Perioperative rVWF Infusion
Excellent (1)	Intra- and post-operative hemostasis achieved with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) was as good or better than that expected for the type of surgical procedure performed in a hemostatically normal subject
Good (2)	Intra- and post-operative hemostasis achieved with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) was probably as good as that expected for the type of surgical procedure performed in a hemostatically normal subject
Moderate (3)	Intra- and post-operative hemostasis with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) was clearly less than optimal for the type of procedure performed but was maintained without the need to change the rVWF (vonicog alfa) concentrate
None (4)	Subject experienced uncontrolled bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of rVWF (vonicog alfa) concentrate

11.6 rVWF Pharmacokinetics and Pharmacodynamics

PK will be assessed twice for all subjects.

For on-demand subjects, an initial PK assessment using a dose of 50 IU ± 5 IU/kg rVWF:RCo will be performed at the baseline visit, and 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 week 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 assay. 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 assessment using the subject's individualized dose will be performed shortly after reaching steady state, which is estimated to be reached for the majority of subjects after approximately 11 days from the 1st prophylactic dose. To fit any logistical requirements, samples for PK analysis can be taken after prophylaxis dose #5-6, and whenever possible, sample collections should be during the longer partial interval of the alternating irregular dosing intervals. For example, if a subject follows a dosing regimen as follows:

Date	Weekday	Dose number	Interval	Time from 1st 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 profile will be assessed at the end of the study, i.e. 12* month ± 2 week visit with a PK 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 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). If the dosing interval for a certain switch subject wouldn't allow for the full 11 post-infusion timepoints sample collection, 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 for an individual switch subject.

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

* Study treatment period is extended by 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.

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

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, whether or not considered causally related to the IP.

12.1.1.1 Serious Adverse Event

An SAE is defined as an untoward medical occurrence that, at any dose, meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are (including but not limited to):
  - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
  - Reviewed and confirmed seroconversion for HIV, hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)

- Development of clinically significant neutralizing VWF antibodies
- Development of neutralizing antibodies to FVIII (titer ≥0.4 BU [by Nijmegen- modified Bethesda assay] or ≥0.6 BU [by Bethesda assay])
- Thromboembolic events (e.g., myocardial infarction, stroke, transient ischemic attack [TIA], deep vein thrombosis [DVT] or pulmonary embolism)
- Hypersensitivity reactions (e.g., anaphylaxis [for definition, refer to Section 12.6.2] and other immediate and delayed hypersensitivity reactions which may manifest with urticarial rash, pruritus, flushing, angioedema of the face, extremities, or laryngeal tissues [leading to throat tightness with stridor], wheezing, gastrointestinal symptoms, and/or hypotension)

Uncomplicated pregnancies, following maternal or paternal exposure to IP are not considered an AE/SAE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE and should be reported per SAE reporting guidelines provided in Section 12.1.2.3 (Safety Reporting).

12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any suspected adverse reaction to study treatment that is both serious and unexpected is considered a SUSAR.

The event(s) must meet all of the following:

- Suspected adverse reaction (which implies that there is reasonable evidence indicating a causal relationship between the event and the study treatment),
- Unexpected (per Reference Safety Information (RSI)/IB), and
- Serious

Once determined to meet the criteria for a SUSAR, the sponsor will ensure expedited SUSAR reporting is completed in line with the regulatory requirements in participating countries as outlined in the Safety Management Plan.

12.1.1.3 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet any of the seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) listed in section 12.1.1.1.

12.1.1.4 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (e.g., IB, PI [prescribing information]). "Unexpected" also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.1.1.5 Preexisting Disease

Preexisting diseases that are present before entry in to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described as "worsening" of the pre-existing condition on the AE CRF.

12.1.2 Assessment of Adverse Events

For the purposes of this study, the following will not be considered as AEs and will not be included in the analysis of AEs.

- Bleeding episodes are part of the underlying disease and therefore are not AEs; they will be evaluated in the context of efficacy.
  - For non-serious bleeding episodes caused by an injury, the injury would not be reported as an AE, unless it resulted in a medical finding other than a bleeding episode (e.g., abrasion of skin). Therefore, any VWD-related bleeding event (e.g., epistaxis, gastrointestinal bleeding, musculo-skeletal bleeding, menorrhagia) that is non-serious will not be reported as an AE. However, the investigator may decide that the event is an AE if the event also would have occurred in a healthy individual under the same circumstances.
  - For serious bleeding episodes (bleeding SAEs): Bleeding events that meet seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) should be captured on the SAE eCRF and reported as an SAE to the Sponsor or designee (e.g., CRO) on an SAE Report form as described in Section 12.1.2.3 (Safety Reporting).
- Seroconversion after documented HAV/HBV vaccination prior to or during the study period.

Each AE from the first IP exposure to the study completion date will be described on the AE CRF using the term representing medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial verbatim expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2

For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable, action taken with regards to the study treatment (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution or until the subject's condition returns to the level at the baseline for pre-existing conditions.

If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the protocol-specified dosage (including underdosing /overdosing [<20 IU/kg rVWF:RCo or >100 rVWF:RCo], abuse, and withdrawal, treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after administration of IP will be reported on a Pregnancy Form and followed-up at 1 year post-delivery, if feasible.

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the SAE Form within 24 hours after awareness: no additional reporting on CRFs is necessary.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, e.g., assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs

- Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP, is not biologically plausible per mechanism of action of the IP, or has a much more likely alternative etiology).

- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of IP
  - An alternative etiology is equally or less likely compared to the potential relationship to the IP
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
    - Reappearance of a similar reaction upon re-administration (positive re-challenge)
    - Positive results in a drug sensitivity test (skin test, etc.)
    - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
  - Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within 5 days after IP infusion, the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

12.1.2.3 Safety Reporting

AEs and SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Section 20.2) and Section 12.1.2.

Adverse Events and SAEs are to be recorded on the AE page of the eCRF. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the IP, must be reported immediately (within 24 hours of the study center's first knowledge of the event). All SAEs must be reported in English via the Electronic Data Capture (EDC) system by completing the relevant eCRF page(s) and also by SAE Report Form via fax/email to Sponsor's Global Drug Safety (Baxalta GDS) department within 24 hours of becoming aware of the event for SAEs (for contacts, instructions, and additional details, refer to the SAER form).

Within 24 hours of site awareness of a SAE (or Pregnancy) study sites will complete and send all SAE (or Pregnancy) reports to a dedicated:

Baxalta Global Drug Safety fax number: [redacted]

OR

email: [redacted]

The responsible Site Monitor will review the SAE (or Pregnancy) Reports for completeness, will reconcile the reports against the EDC database, and will follow-up with sites to obtain missing information and/or information requiring clarification. Any SAE associated with a pregnancy must be reported on the SAER Form.

For Follow-up Reports, the site shall use a new SAER form (marked as Follow-up) and the new information should be entered together with a brief narrative identifying the updated data.

An SAER should include the following minimum information:

1. Protocol Number (on all pages)
2. Subject identification number (on all pages) and demographics (gender, age at onset of event and/or date of birth)
3. Investigational product and treatment regimen (including date of the first dose of IP, date of the last dose of IP prior to the onset of the SAE)
4. Medical Term for Event (Diagnosis preferably)
5. Description of the SAE, including:
    - Date of onset
    - Causal relationship assessment by the Investigator
6. Seriousness criteria (e.g., death, life-threatening, hospitalization, medically significant, or other criterion)
7. Name, address, fax number, email, and telephone number of the reporter/Investigator

Post-trial SAE Reporting: In compliance to EudraLex Volume 10 (Clinical trials guidelines, Chapter II: Safety Reporting from the European Commission), which references an EMA guidance (ICH Topic E 2 A - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting), clinical sites/the investigator should report to the Sponsor SAEs after a subject´s study completion. Study sites will be provided a Post-Trial SAER form to complete and report these post-study SAEs to the Sponsor within the 24 hours of their awareness. Site Monitor will instruct the site that any such Post-Trial SAEs should be reported on the study-specific Post-Trial SAER form if/when the site becomes aware of it. Such information will not be actively monitored by the sponsor after completion of the study.

These events shall be reported to Baxalta GDS who will process them in the same way as SAEs occurring during the study. Post-Trial SAEs do not need to be captured in the study EDC database if it is already locked. Irrespective if captured in the EDC database or not, such Post-Trial SAEs will become part of the GDS database. The monitor should remind the clinical site about the post-trial SAE reporting requirements during interim monitoring visits, upon each subject's study completion as well as during the close-out visit.

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of the clinical trial
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor.
In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committees (ECs) and relevant competent authority(s) are notified of the urgent measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (i.e., from the time of signed informed consent up to but not including the first IP exposure) will be described on the SAER. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE.** NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g. reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (e.g., potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) 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. The subject's medical history will also include documented history of on-demand or pdVWF prophylaxis treatment for at least the past 12 months and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 months (up to 24 months if available).

All medications taken and non-drug therapies received in the 2 weeks prior to study entry and all concomitant medications and non-drug therapies during study will be recorded on the CRFs.

Data on medical history, drug and non-drug therapy history of those subjects who transition from surgery rVWF (vonicog alfa) study will be used from the eCRF of the main studies, will be updated, if applicable, and transcribed into the respective eCRF of the prophy study.

12.6 Physical Examinations

At screening and subsequent study visits (as described in Section 10.3), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 12.1.1.5), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.6.1 Thromboembolic Events

There is a risk of occurrence of thrombotic events, particularly in patients with known clinical or laboratory risk factors for thrombosis including low ADAMTS13 levels. Therefore, patients at risk must be monitored for early signs of thrombosis during the study and prophylaxis measures against thromboembolism should be instituted according to current recommendations and standard of care. Additional diagnostic procedures are required according to each institution's standard of care which may consist of, but are not limited to the following:

- For DVT: Magnetic Resonance Imaging (MRI), compression ultrasound or impedance plethysmography.
- For pulmonary embolism: ECG, chest radiography, perfusion/scintiscan or MRI.
- For myocardial infarction: ECG, cardiac enzymes, echocardiography
- For stroke: diffusion-weighted magnetic resonance imaging or computed tomography, ABCD scoring, carotid imaging

Results of diagnostic procedures may be forwarded to the sponsor to be reviewed by an independent external expert panel, such as the DMC, if applicable.

12.6.2 Anaphylaxis

The diagnosis of anaphylaxis is highly likely when any of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g, generalized urticaria, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
    b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a. Involvement of the skin or mucosal tissue (e.g., generalized urticaria, pruritus or flushing, swollen lips-tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c. Reduced BP or associated symptoms (hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to a known allergen for that patient (minutes to several hours):
    a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
    b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP

If a subject develops anaphylaxis in the course of the clinical study, this needs to be reported as SAE (Section 12.1.1.1). Additional blood will be drawn for Anti-VWF IgE antibody testing (Section 12.9.13).

12.7 Vital Signs

Vital signs will be assessed pre- and post-infusion at each visit, if not stated otherwise:

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

Vital signs (pulse rate, respiratory rate, and blood pressure) should be recorded within 30 min before and after IP administration. The assessment of vital signs per planned study visit is outlined in Supplement 20.2.

Vital sign values are to be recorded on the physical examination eCRF. For each vital sign value, the investigator will determine whether the value is considered an AE (see definition in Section 12.1). If assessed as an AE, the medical diagnosis (preferably), symptom, or sign, will be recorded on the AE eCRF. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE, should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.8 Electrocardiogram

A standard 12-lead ECG at rest will be performed at screening, at the 6 month follow-up visit and at the study termination visit and evaluated for medical significance by the investigator.

12.9 Clinical Laboratory Parameters

Refer to the Laboratory Manual for information on collection and processing of samples.

In general all laboratory tests will be performed at central laboratories, except the pregnancy and blood group test which will be performed at the local laboratory. In addition, relevant critical safety laboratory tests for complete blood count (CBC), serum chemistry and/or coagulation parameters such as VWF and FVIII activity may also be performed in the local laboratory to ensure that results will be available immediately to the investigator. In principle, results from the central laboratory will be used for data analysis purposes. The assays performed in the central laboratories are specified in the Laboratory Manual. The investigator will supply the sponsor with a list of the normal ranges and units of measurement for the laboratory variables to be determined at the site. Laboratory values such as antibodies to other proteins are not required immediately and will be assessed later during the course of the study.

Any abnormal laboratory value that is considered clinically significant by the investigator based on a local laboratory test result (reference range and the units to be provided) should be confirmed by a central laboratory test result for which the sample is drawn/collected within 24 hours of the abnormal finding by the local laboratory.

12.9.1 rVWF Pharmacokinetics and Pharmacodynamics

Details on pharmacokinetic and pharmacodynamics assessments are provided in Section 11.6.

12.9.2 Hematology and Clinical Chemistry

The hematology panel will consist of CBC [hemoglobin, hematocrit, erythrocytes (ie, red blood cell count [RBC]; mean corpuscular volume [MCV], mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration [MCHC]), and leukocytes (i.e., white blood cell count [WBC])] with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.

The clinical chemistry panel will consist of sodium (Na), potassium (K), chloride (Cl), ALT, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase (AP), blood urea nitrogen (BUN), CR, and glucose (Glu).

Blood will be obtained for assessment of hematology and clinical chemistry parameters at screening, during PK-assessment prior to rVWF (vonicog alfa) IP infusion, after 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours post rVWF (vonicog alfa) IP infusion, at all follow-up visits as per schedule (refer to Supplement 20.3 Clinical Laboratory

Assessments), i.e., 4 weeks ± 1 week, 8 weeks ± 1 week and every 3 months ± 2 weeks, and at study completion. Hematology and clinical chemistry assessments will be performed on Ethylenediaminetetraacetic acid (EDTA)-anticoagulated whole blood and serum, respectively, at the central laboratory.

12.9.3 Immunology

12.9.3.1 Antibodies to VWF and FVIII

All subjects will be tested for binding and neutralizing antibodies to VWF and FVIII at screening, at initial PK assessment, at each of the scheduled follow-up visits and at the study completion visit. Testing will be done prior to IP infusion and with at least a 72 hour wash out period since the last IP infusion. If there is any suspicion of inhibitor development (e.g. excessive bleeding) binding and neutralizing antibodies to VWF and FVIII may be tested at the discretion of the investigator.

12.9.3.2 Neutralizing and Total Binding Anti-VWF Antibodies

The assays to establish the presence of neutralizing and total binding anti-VWF antibodies have been established in the absence of international standards and with only limited numbers of positive controls. Therefore, caution is advised in interpreting positive results. In particular, any clinical association, changes in the natural history of the disease, effect of therapy, etc. needs to be taken into account for final judgment. The sponsor's Medical Director should be consulted for additional advice. As part of the AE follow-up, any sample testing positive needs to be confirmed after 2-4 weeks for central laboratory testing. Only confirmed neutralizing anti -VWF antibodies are considered inhibitors (see Section 12.9.3.4). These subjects need to be closely monitored and therapy adjusted accordingly.

12.9.3.3 Binding antibodies to VWF

The presence of total binding anti-VWF antibodies will be determined by an enzyme-linked immunosorbent assay (ELISA) employing polyclonal anti-human Immunoglobulin (Ig) antibodies (IgG, IgM and IgA). For this assay (ELISA), recombinant human VWF will be coated onto a microtiter plate, then incubated with dilutions of the positive control, the negative control or test sample. Antibodies against human VWF that are present in the samples bind to the coated antigen and will be detected with a horseradish peroxidase (HRP)-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a human monoclonal antibody specific for human VWF spiked into the negative control. The negative control for this assay is pooled normal human plasma.

Plasma samples are analyzed for binding antibodies against the specific antigen in two steps. First, the sample is screened for antibodies and the titer of binding antibodies is determined. Second, the specificity of positive antibody results is confirmed.[16]
In brief, all samples are serially diluted (initial dilution 1:20 and further diluted 1:2).

The titer endpoint, defined as the highest dilution that still gives a positive signal above cut off level, is determined in two independent duplicates. The cut off level is established based on background signal level of healthy plasma donors (n=160) and set to include 5% false positives to be as sensitive as possible (95% percentile). The ELISA assay is validated allowing an assay variability of ± 1 titer step. Therefore, differences ≤ 2 titers steps may be due to variability of the ELISA assay. Specificity has to be confirmed in a competition assay when a sample has a titer of 1:80 or higher in the screening assay. Based on the validation criteria samples tested in the screening assay at 1:20 or 1:40 cannot be confirmed in the competition assay. A positive screening value is confirmed if the difference between the titers determined for the subject sample (re-screen) and for the subject sample with pre-incubation (confirmation sample) is > 2 titer steps. Antibody titers of subject samples will only be reported as positive, if the results of the screening and confirmatory analysis fulfill these acceptance criteria. The titer to be reported is always the one determined in the original screening procedure (independent of the result of the re-screening in the confirmation procedure).

A more detailed test procedure will be supplied upon request or pro-actively if a sample tests positive. A treatment related increase of the binding anti-VWF antibodies is expected, if the titer increases by more than 2 titration steps. These subjects need to be closely monitored and therapy adjusted accordingly.

12.9.3.4 Neutralizing Antibodies to VWF

Three functional VWF assays, VWF:CB, VWF:RCo and VWF:FVIIIB assays, will be used to test for the presence of neutralizing anti-VWF antibodies. Neutralizing antibodies to VWF:RCo, VWF:CB and VWF:FVIIIB activities will be measured by assays based on the Bethesda assay established for quantitative analysis of FVIII inhibitors (Nijmegen modification of the Bethesda assay).[17] The amount of inhibitor is expressed as BU per mL. One BU is thereby defined as the amount of inhibitor that decreases the measured activity in the assays to 50% of that of the negative control samples. The assays were validated using human plasma samples from two type 3 VWD patients with low (1-2 BU/mL) and high (~10 BU/mL) titer inhibitors and plasma samples from non-human primates immunized with human rVWF (vonicog alfa) (>100 BU/mL).

If a subject has a measurable baseline level of VWF activity in the respective assay, it is taken into account in the calculation of the residual activity. However, if baseline levels are too high (>15% VWF:RCo), inhibitors may not be reliably detected.

To exclude false positive results, the detection limit for anti-VWF inhibitors was set to 1 BU/ml for all 3 assays. The rationale for this cut-off value is the relatively high CI of the underlying assays, making determinations at the end of the evaluation range of the Bethesda reference curve uncertain.[18] A more detailed test procedure may be requested to further characterize the anti-VWF inhibitors, if detected.

Only confirmed positive anti-VWF inhibitor test result will be reported and will be considered as a medically significant SAE.

12.9.3.5 Binding Antibodies to FVIII

Binding antibodies against FVIII will be analyzed using a proprietary enzyme immunoassay. The testing strategy will be as described for binding anti-VWF antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.3.6 Neutralizing Antibodies (Inhibitors) to FVIII

Neutralizing antibodies (inhibitors) to FVIII will be assessed by the Nijmegen modification of the Bethesda assay in a central laboratory. To verify a FVIII inhibitor, additional testing (such as tests for Lupus anticoagulants) may be initiated. Positive FVIII inhibitor tests will be defined as $\geq$ 0.4 BU by the Nijmegen-modified Bethesda assay that is confirmed by a second test performed on an independent sample obtained 2-4 weeks following the first test. Only confirmed positive FVIII inhibitor test result will be reported.

12.9.4 Antibodies to Other Proteins

Plasma will be assayed for the presence of antibodies against CHO protein (total Ig), murine IgG and human Furin (total Ig) using proprietary enzyme immunoassays. The testing strategy will be as described for binding anti- VWF antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.4.1 Anti-CHO Protein

Total Ig antibodies (IgG, IgA, IgM) against CHO protein will be analyzed. For this assay (ELISA), CHO protein derived from cultures of untransfected cells and propagated under the identical cell culture conditions used for ADVATE (rFVIII, octocog alfa) production will be coated onto a microtiter plate, then incubated with dilutions of the positive control, negative control or test sample. Antibodies against CHO protein that are present in the samples bind to the coated antigen and will be detected with a HRP-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a polyclonal goat anti-CHO protein antibody spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.4.2 Anti-Murine IgG

A commercially available ELISA (Medac, Hamburg, Germany) will be used to detect and to quantify IgG antibodies originating from human plasma that are directed against mouse-IgG (HAMA: human anti- mouse antibodies). Microtiter plates coated with mouse IgG will be incubated with dilutions of the standard, the positive control, the negative control or the test sample. Antibodies against mouse IgG that are present in the samples bind to the coated antigen and form a bridge to a peroxidase coupled mouse IgG antibody that will be used for detection (bridging format of the ELISA assay). The positive control for this assay will be a polyclonal goat anti-murine IgG spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.4.3 Antibodies to Human Furin

Total Ig antibodies (IgG, IgA, IgM) against human Furin will be analyzed. For this assay (ELISA), recombinant human Furin will be coated onto a microtiter plate, then incubated with dilutions of the positive control, the negative control or test sample. Antibodies against human Furin that are present in the samples bind to the coated antigen and will be detected with a HRP-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a human monoclonal antibody specific for human Furin spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.5 Viral Serology

The following viral seromarkers will be assessed at screening:

- HIV: anti-HIV 1, HIV 2
- HAV: anti-HAV (IgG and immunoglobulin M [IgM])
- HBV: Hepatitis B surface antigen (HbsAg), anti-Hepatitis B (HB) core, anti-HBs

- HCV: anti-HCV ELISA
- Parvovirus B19: anti-B19V (IgG and IgM)

Virus serology will be established during the screening period. The relevant confirmatory Polymerase Chain Reaction (PCR) testing may be performed from appropriate left-over samples as needed.

12.9.6 Urinalysis (Dipstick)

The urinalysis will include assessments for erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite and pH and will be performed at the central laboratory.

12.9.7 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. The pregnancy test may need to be repeated during the course of study in countries where mandated by national law.

12.9.8 VWD Mutational Analysis, Multimer Analysis and Human Leukocyte Antigen Genotyping

A cell pellet (buffy coat and erythrocytes) will be retained at the screening visit for VWD gene mutational analysis, VWF multimer analysis and HLA genotype determination if the information is not already available in the subject's medical history. Results from multimer analysis (see Section 12.9.10.1) may contribute to VWD gene mutational analysis. The genetic testing will be done, when the subject consents to the genetic testing.

12.9.9 Blood Group Analysis

The blood group needs to be determined during the screening period. If the information is not already available in the subject's medical history, it has to be determined at the local lab.

12.9.10 Additional Laboratory Testing in Case of Thromboembolic Events

rVWF (vonicog alfa) contains ULMW multimers because of a lack of exposure to endogenous VWF protease (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) during the manufacturing process. In vitro and in vivo cleavage of these ultralarge molecular fractions by ADAMTS13 and generation of characteristic satellite bands has been extensively demonstrated during nonclinical and clinical development. Nevertheless, the potential elevated risk of thrombosis and/or other thromboembolic complications due to the administration of ultra large molecular VWF multimers in subjects with normal levels of VWF cannot be completely excluded. Therefore VWF multimer analysis will not only be performed routinely at screening but in case of thromboembolic events, both VWF multimer analysis as well as ADAMTS13 activity will be determined to assess any relatedness of these occurrences with IP treatment.

12.9.10.1 VWF Multimer Analysis

The VWF multimer pattern will be assessed using low-resolution sodium dodecyl sulfate (SDS)–agarose gel electrophoresis. High-resolution SDS–agarose gel electrophoresis, with agarose concentrations >1.5%, will be used to determine the satellite band structure of VWF. These analyses will employ Western blot with luminescence video imaging.

12.9.10.2 ADAMTS13 Activity

VWF73 was identified as the 73 amino acid minimal region of the VWF A2 domain required for ADAMTS13 cleavage. The cleavage of this substrate will be detected by a commercially available ELISA-based Chromogenic assay (Technoclone Austria): Cleavage of immobilized VWF73 substrate is detected by a HRP-labeled antibody directed against the cleavage site of VWF73. The amount of bound antibody, which is the function of the ADAMTS13 cleavage is detected by a chromogenic substrate.

12.9.11 Soluble P-Selectin (sP-Selectin)

sP-selectin is a cell adhesion molecule (CAM) found in granules in endothelial cells (cells lining blood vessels) and activated platelets. Data for an association between the sP-selectin concentration, TTP and venous thromboembolism (VTE) are limited and the predictive value has not yet established. A commercial ELISA assay will be employed as an exploratory test. sP-selectin will be determined at the Screening visit and used as indicator for an increased thrombotic risk.

12.9.12 D-Dimer

D-dimer will be used as a marker for DVT and disseminated intravascular coagulation (DIC). While a negative result practically rules out thrombosis, a positive result can indicate thrombosis but does not rule out other potential etiologies, including a recent hemorrhage. Its main use, therefore, is to exclude thromboembolic disease where the probability is low. D-Dimer will be measured at the Screening visit and used as indicator for an increased thrombotic risk.

12.9.13 Additional Laboratory Testing in Case of Severe Hypersensitivity Reactions

If a subject develops a severe hypersensitivity reaction in the course of the clinical study, additional blood will be drawn for anti-VWF IgE antibody testing. The presence of anti-VWF IgE will be determined by using the ImmunoCAP®, a VWF-specific IgE blood test (Thermo Scientific). The basis of the ImmunoCAP® technology is a cellulose polymer as solid phase in a plastic capsule providing a large surface for protein binding. rVWF (vonicog alfa) as antigen is covalently coupled to the cellulose polymer.

Detection of specific anti-VWF IgE bound to the antigen will be accomplished by a secondary enzyme-labeled anti-human IgE antibody. Testing for binding anti-human VWF IgE antibodies will be done with 0.5 mL plasma. Antibody containing samples will be identified and quantified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.14 Assessment of Laboratory Values

12.9.14.1 Assessment of Abnormal Laboratory Values

For VWF and FVIII laboratory assessments no evaluation of clinical significance is necessary.

Each other laboratory value (except results to determine genetics of the underlying VWD disease and blood group) has to be assessed by the investigator and the assessment will be recorded on the eCRF. The investigator will determine for each abnormal laboratory value whether the value is considered clinically significant or not and provide the reference range including the units. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 12.1) and record the sign, symptom, or medical diagnosis on the AE CRF, is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.5), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, i.e. because it is due to a preexisting disease, due to a lab error, due to variation or due to another issue that will be specified.

Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator. Any abnormal laboratory value that is considered clinically significant by the investigator based on a local laboratory test result (reference range and the units to be provided) should be confirmed by a central laboratory test result for which the sample is drawn/collected within 24 hours of the abnormal finding by the local laboratory.

Any seroconversion result for HIV, HAV, hepatitis B virus (HBV), HCV, HEV, or B19V shall be re-tested.

12.10 [redacted]

12.10.1 [redacted]

12.10.2 [redacted]

[redacted]

13. STATISTICS

13.1 Sample Size and Power Calculations

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 cohort (OD and switch). A total of at least 5 type 3 VWD subjects will be followed for 12 months. 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).[1]

13.2 Datasets and Analysis Cohorts

13.2.1 Safety Analysis Set

The Safety Analysis Set will be composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

13.2.2 Full Analysis Dataset

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

13.2.3 Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set will be composed of subjects who are at least 70% compliant regarding the number of scheduled prophylactic infusions (as measured by the ratio of actual number of infusions to planned number of infusions). Only subjects who met all study entry criteria and who had no major protocol violations that might impact primary efficacy assessments will be included in the PP analysis set.

13.2.4 PK Full Analysis Set

The Pharmacokinetic Full Analysis Set (PKFAS) will be composed of all subjects who received the PK infusion and who provided acceptable data for PK and PD analysis. Acceptable PK/PD data will be defined in the Statistical Analysis Plan.

13.2.5 PK Per Protocol Analysis Set

The Pharmacokinetic 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 affecting the PK period of the study as defined in the detailed Statistical Analysis Plan.

13.3 Handling of Missing, Unused, and Spurious Data

13.3.1 General

Statistical techniques will not be used to identify and exclude any observations as outliers from the analyses. If data are considered spurious, e.g. for lack of biological plausibility, it will be documented to include the reason for exclusion and the analyses from which the data were excluded.

13.3.2 Other

1. Regarding missing data in PK records:
    - Body weight: If a subject's weight is missing from the PK infusion record, the subject's last recorded weight will be used to calculate the weight-adjusted dose.
    - Concentration:
        - Baseline concentration levels reported as below the limit of quantification will be considered to be 0. Missing VWF baseline concentration levels (VWF: RCo, VWF: AG or VWF: CB) for Type 3 subjects will be set to 0.
    - Time:
        - If start time of infusion is missing (but stop time is available) and actual collection time is available, then stop time of infusion will be taken for further calculation (i.e. time difference between actual end date/time of infusion and date/time blood sample drawn).
        - If actual collection date/time is missing and planned collection date/time is missing, then this PK time point will be taken out from the PK analysis (i.e. no data entry for this time point).
        - For all other scenarios, the planned collection date/time will be taken for further calculation.
2. Regarding missing data in AE records:
    - Handling of unknown causality assessment:
        - If a subject experiences an AE with a missing causality assessment, the relationship of the AE will be counted as "related."

- Handling of unknown severity grades:
  - If a subject experiences more than one AE categorized under the same preferred term, 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.

13.4 Methods of Analysis

The study success criteria are the objectives as stated in Section 7. “Treatment success” was defined as the extent of control of bleeding episodes achieved during this study.

13.4.1 Primary Outcome Measure

The primary outcome measure is ABR for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa). No formal statistical hypothesis test is planned for the analysis. The primary efficacy analysis will be based on the FAS and will be summarized by the two cohorts: on-demand and switch subjects. As a supportive analysis, the same analysis will also be carried out on the PP analysis set.

The spontaneous ABR while treated with rVWF (vonicog alfa) for each cohort will be estimated using a negative binomial regression. The prior ABR will be based on historical data collected from each enrolled subject.

The two ABRs (prior to prophylaxis treatment and while on prophylaxis) for each cohort will be compared within each subject using a generalized linear mixed-effects model (GLMM) (with a logarithmic link function, the default for the negative binomial distribution), accounting for the fixed effect of the two treatments. The follow-up time (in years) will be specified as an offset. The ratio of ABR while in the study to historical ABR will be estimated and reported together with the 95% confidence interval for each of the two cohorts.

The difference in on-study ABR relative to historical ABR will be also summarized descriptively.

13.4.2 Secondary Outcome Measures

In general, data for secondary efficacy analysis will be summarized by the two cohorts: on-demand and switch subjects and when applicable overall. Mean, standard deviation, median, range, quartiles will be calculated for continuous endpoints. Proportions, will be calculated for categorical endpoints. Confidence intervals at the two-sided 95% level will be provided when appropriate.

13.4.2.1 Additional Efficacy of Prophylaxis Treatment with rVWF

The number and proportion of on-demand subjects with ABR percent reduction success (i.e.≥ 25%) will be calculated together with a two-sided, 95% CI for the proportion.

The number and proportion of pdVWF switch subjects ABR preservation success will be reported together with the corresponding 95% two-sided CIs for the proportion.

The number and proportion of subjects with categorized spontaneous ABR (i.e. 0, 1-2, 3-5, more than 5 bleeds) will be reported descriptively.

Summary statistics for the total number of infusions, as well as average number of infusions per week will be provided. The total weight adjusted consumption of rVWF (vonicog alfa) during prophylactic treatment will be provided. If applicable, historical data on consumption of pdVWF prior to the study will be summarized as well.

The change in spontaneous ABR from the historical rate to that during the rVWF (vonicog alfa) prophylaxis period will be summarized by location of bleeding (GI, epistaxis, joint bleeding, menorrhagia, oral and other mucosa, muscle and soft tissue, etc.).

13.4.2.2 Pharmacokinetic and Pharmacodynamic Analysis

All PK and PD analyses will use the actual sampling times, not nominal times specified in the protocol, wherever possible. Actual sampling times will be defined as time from the start of infusion to the blood sample collection time. A deviation from the protocol-specified blood sample 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 results were biologically implausible will be eliminated from the analysis.

If any concentration data are considered spurious (e.g. lack of biological plausibility), the reason for exclusion from the analysis and the analysis from which the data point was excluded will be documented.

Details of calculation of PK and PD parameters and corresponding analysis will be given in the statistical analysis plan.

The following PK parameters, based on the initial PK assessment after a washout for on-demand subjects, will be listed and summarized descriptively for VWF:RCo, VWF:Ag and VWF:CB: IR, $T_{1/2}$, MRT, $AUC_{0-\infty}$, $AUC_{0-tlast}$, C_{max}, T_{max}, V_{ss}, and CL. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity, based on the initial PK assessment after a washout for on-demand subjects will be assessed using C_{max}, T_{max}, and $AUC_{0-tlast}$. These PD parameters will be listed and summarized descriptively. PK parameters at steady state ($AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$) for the partial dosing interval will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study for VWF:RCo, VWF:Ag and VWF:CB and summarized descriptively for subjects with the same dosing regimens. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity will be assessed using $AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$. These PD parameters will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study and will be summarized descriptively for subjects with the same dosing regimens.

For the on-demand subjects, the PK of VWF:RCo will be analyzed using a population PK approach to characterize the single and multiple dose pharmacokinetics, including associated variability assessed at after washout and at end of study, respectively. The population PK analysis will be performed in a stepwise manner as outlined below.

1. Exploratory graphical analysis of VWF:RCo versus time data for identification of potential outliers and to inform the pharmacometric analysis.
2. Population PK model development for rVWF (vonicog alfa):
    a. Evaluate alternative structural and stochastic models to describe the typical and individual rVWF (vonicog alfa) profiles.
    b. Investigate and characterize the potential for a time dependency in CL of rVWF (vonicog alfa).
    c. Evaluate, and if necessary refine, the candidate final model

Details of this Population PK analysis will be given in a separate Population PK analysis plan.

For the switch subjects, differences in $AUC_{0\text{-}tau;ss}$, $C_{max;ss}$, and $C_{min;ss}$ assessess shortly after reaching steady state and assessed at the end of the study will be assessed by the ratio of geometric means and corresponding two-sided 95% confidence intervals for VWF:RCo, VWF:Ag,VWF:CB, and FVIII:C. These analyses will be performed using a linear mixed effects model with PK assessment (i.e. factor of two levels relating to the PK assessment shortly after reaching steady state and the PK assessment at end of study, respectively) as a fixed effect and subject as a random effect based on log-transformed PK parameters. 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.

Descriptive statistics will be used to summarize VWF:RCo, VWF:AG and VWF:CB and FVIII:C levels for each nominal time point on the PK curve.

For all subjects in the PKFAS activity/concentration vs. time curves will be prepared.

Formulas for PK parameters IR, $T_{1/2}$, MRT, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}tlast}$, C_{max}, T_{max}, V_{ss}, and CL, $AUC_{0\text{-}tau;ss}$, $C_{max;ss}$, $T_{max;ss}$,and $C_{min;ss}$ will be given in the statistical analysis plan and will be derived using non-compartmental methods in WinNonlin. Analysis of these parameters will be carried out on the PKFAS as well as on the PKPPAS.

13.4.2.3 Safety

Safety analysis will be performed overall and by the two cohorts: on-demand and switch subjects.

TEAEs are defined as AEs with start dates on or after the first exposure to IP. Summaries of AEs will be based on TEAEs unless otherwise indicated.

Occurrence of AEs and SAEs will be summarized descriptively, by system organ class and preferred term. The number and percentage of subjects who experienced AEs and SAEs, and the number of AEs and SAEs will be tabulated. In addition, the number of subjects who experienced AEs assessed as related to IP by the investigator, and the number of IP-related AEs will be tabulated. The number of patients with AEs by severity will be presented similarly.

A listing of all AEs will be presented by subject identifier, age, sex, preferred term and 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.

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 infusion, irrespective of being related or not related to treatment. Temporally associated AEs will be presented in summary tables.

AEs that occurred before first IP infusion will be listed separately.

Adverse events of special interest (AESI), such as hypersensitivity reactions and thromboembolic events, will be monitored throughout the study and statistical analysis will be conducted based on the search criteria (eg, standardised MedDRA queries [SMQ]) determined prior to database lock, and summarized.

For immunogenicity, frequency counts and percentages will be calculated for 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. Clinically significant changes relative to baseline in vital signs and clinical laboratory parameters (hematology, clinical chemistry) will be reported.

13.4.3 Exploratory Outcome Measures

[redacted]

13.4.3.1 [redacted]

[redacted]

13.4.3.2 [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

13.4.3.3 [redacted]

[redacted]

13.4.3.4 [redacted]

[redacted]

13.5 Planned Interim Analysis of the Study

No formal interim analysis is planned for this study.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Trial Agreement (CTA). If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the CTA.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable national and local regulatory requirements as described in the CTA. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

15.1.1 Investigator Report and Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the CTA. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the CTA. Auditing processes specific to the study will be described in the audit plan.

15.5 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. Also, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing whenever pdVWF is used instead of rVWF (vonicog alfa). The reason for this use must also be provided to the sponsor.The sponsor (Baxalta) will also ensure the responsible EC and relevant competent authority are notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.6 Laboratory and Reader Standardization

A central laboratory/reader will be used for all clinical assessments except for pregnancy testing and blood group test (refer to Section 12.9). Local laboratories are requested to provide their laboratory specifications of the individual tests that are also being tested locally.

16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the CTA.

16.2 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the CTA.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

16.3 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients and/or their legally authorized representative must sign an informed consent form before entering into the study according to applicable national and local regulatory requirements and ICH GCP. Before use, the informed consent form will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 16.2). The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable national and local regulatory requirements. Patients or their legally-authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent form, patients or their legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised informed consent form, which have been approved by the applicable EC and regulatory authorities, will be provided by the investigator to the subjects who consented to participate in the study

16.4 Data Monitoring Committee

This study will be monitored by a DMC. The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. 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 stop a trial if it finds toxicities or if treatment is proven to be not beneficial. Details will be defined in the DMC charter.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the CTA.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.7), records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, CRFs, SAERs, laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

If electronic format CRFs are provided by the sponsor, only authorized study site personnel will record or change data on the CRFs. If data is not entered on the CRFs during the study visit the data will be recorded on paper and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (e.g., ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the CTA.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the CTA.

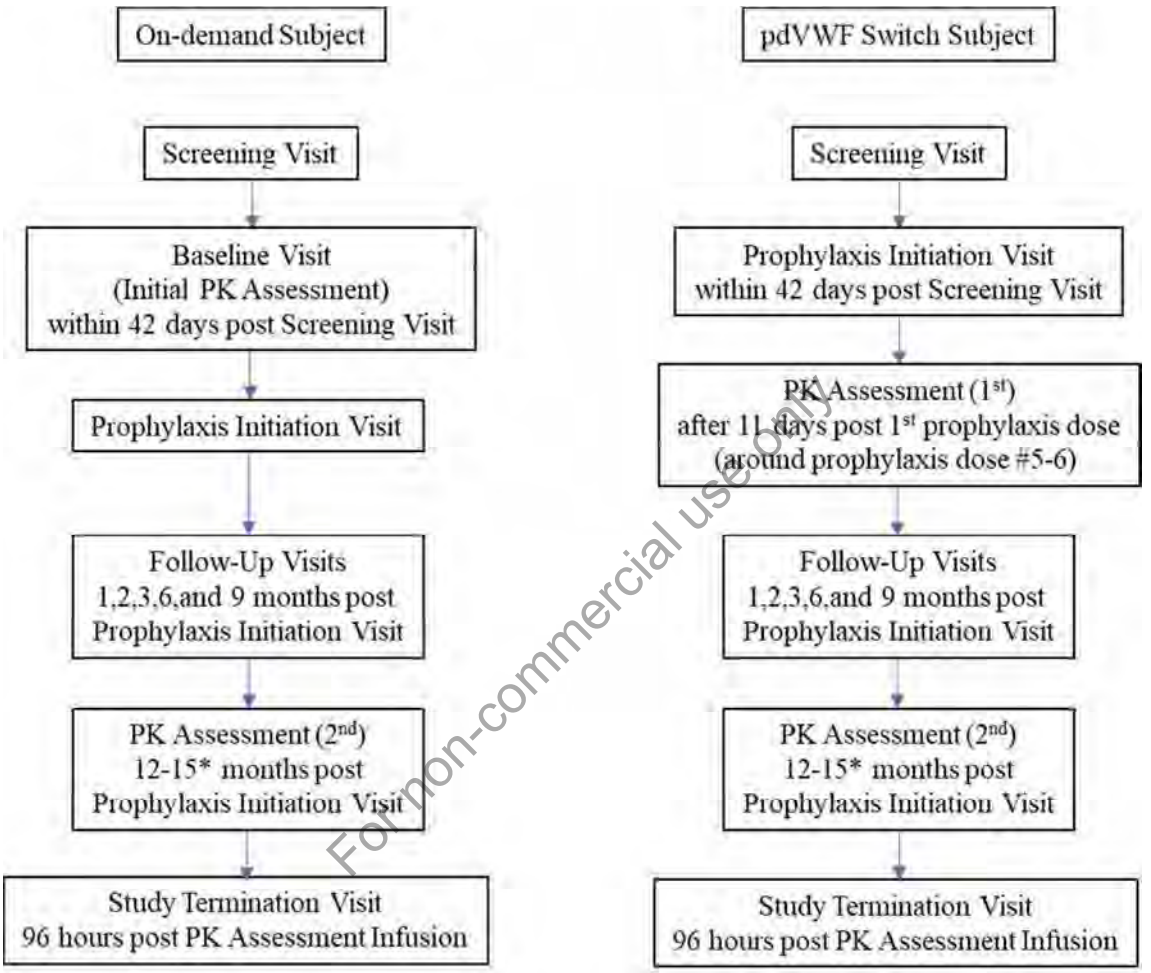
19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the CTA.

20. SUPPLEMENTS

20.1 Study Flow Chart

Figure 1
Study Design for Baxalta Clinical Study 071301



* Study treatment period is extended by 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.

20.2 Schedule of Study Procedures and Assessments

Table 6a
Schedule of Study Procedures and Assessments for On-demand Subject

Procedures/ Assessments	Screening Visit	Baseline Visit (PK-assessment visit)			Prophylaxis Initiation Visit	Interval/Follow-Up Study Visits					PK Assessment at Study Completion			Termination Visit
		Pre-infusion[g]	Infusion	Post-infusion[g]		1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion[g]	Infusion	Post-infusion[g]	Conducted at the 96 hour postinfusion PK Assessment
											12-15[i] month ± 2 weeks			
Informed Consent [a]	X													
Eligibility Criteria	X													
Medical History[b]	X													
Concomitant Medications[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-drug Therapies[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X			X	X	X	X	X	X	X			X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Bleeding Episodes and Treatment and Hemostatic Efficacy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratories	X	X		X	X[h]	X	X	X	X	X	X		X	X
Vital Signs[d]	X	X		X	X	X	X	X	X	X	X		X	X
ECG	X								X					X
IP Treatment[e]			X		X	X	X	X	X	X		X		
IP Consumption / Treatment Compliance						X	X	X	X	X				
Subject Diary					X	X	X	X	X	X				
[redacted]	X[f]								X					X

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Continued

[a]) Occurs at enrollment (before screening).
[b]) Including documented history of on-demand treatment for the past 12 months (up to 24 months if available) and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 (up to 24) months.
[c]) Including all medications and non- drug therapies taken in the 2 weeks prior to study entry and all the concomitant medications and non-drug therapies during the course of the study.
[d]) Vital signs: height, weight, body temperature, pulse rate, respiratory rate, and blood pressure. Height is only required at the screening visit. The time points for pre- and post-infusion measurements are (weight is measured pre-infusion only): within 30 minutes before infusion start and 30 ± 15 minutes post-infusion.
[e]) IP treatment after the prophylactic treatment initiation visit at the site will be continued as home-treatment if the subject qualifies; a wash-out period of at least 72 hours is required after the last IP infusion before the follow-up visit. IP infusion will be given at the study site after the blood sample for immunology testing and IR determination is drawn.
[f]) Can be done either at the screening or the baseline visit.
[g]) Time points for PK blood draws: 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 (the 96 hr sampling can be omitted if not allowed by the dosing interval).
[h]) If a subject did not undergo PK assessment, laboratory assessments will be performed at this visit.
[i]) Study treatment period is extended by 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. In this case, 12 month ± 2 weeks visit is to be considered as a follow-up visit, and EOS visit is to be performed once the subject can rollover into the continuation study, from 12 month ± 2 weeks to 15 month ± 2 weeks post prophylaxis initiation visit, as applicable.

Table 6b
Schedule of Study Procedures and Assessments for pdVWF Switch Subject

Procedures/ Assessments	Screening Visit	Prophylaxis Initiation Visit	PK Assessment (at prophylaxis dose #5-6)			Interval/Follow-Up Study Visits					PK Assessment at Study Completion			Termination Visit
			Pre-infusion[g]	Infusion	Post-infusion[g]	1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion[g]	Infusion	Post-infusion[g]	Conducted at the 96 hour postinfusion PK Assessment
											12-15[h] month ± 2 weeks			
Informed Consent [a]	X													
Eligibility Criteria	X													
Medical History[b]	X													
Concomitant Medications[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-drug Therapies[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X	X			X	X	X	X	X	X			X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Bleeding Episodes and Treatment and Hemostatic Efficacy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratories	X	X	X		X	X	X	X	X	X	X		X	X
Vital Signs[d]	X	X	X		X	X	X	X	X	X	X		X	X
ECG	X								X					X
IP Treatment[e]		X		X		X	X	X	X	X		X		
IP Consumption / Treatment Compliance						X	X	X	X	X				
Subject Diary		X				X	X	X	X	X				
[redacted]	X[f]								X					X

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Continued

[a]) Occurs at enrollment (before screening).
[b]) Including documented history of prophylaxis treatment for the past 12 months (up to 24 months if available) and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 (up to 24) months.
[c]) Including all medications and non- drug therapies taken in the 2 weeks prior to study entry and all the concomitant medications and non-drug therapies during the course of the study.
[d]) Vital signs: height, weight, body temperature, pulse rate, respiratory rate, and blood pressure. Height is only required at the screening visit. The time points for pre- and post-infusion measurements are (weight is measured pre-infusion only): within 30 minutes before infusion start and 30 ± 15 minutes post-infusion.
[e]) IP treatment after the prophylactic treatment initiation visit at the site will be continued as home-treatment if the subject qualifies; a wash-out period of at least 72 hours is required after the last IP infusion before the follow-up visit. IP infusion will be given at the study site after the blood sample for immunology testing and IR determination is drawn.
[f]) Can be done either at the screening or the prophylaxis initiation visit.
[g]) Time points for PK blood draws: 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 (the 96 hr sampling can be omitted if not allowed by the dosing interval).
[h]) Study treatment period is extended by 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. In this case, 12 month ± 2 weeks visit is to be considered as a follow-up visit, and EOS visit is to be performed once the subject can rollover into the continuation study, from 12 month ± 2 weeks to 15 month ± 2 weeks post prophylaxis initiation visit, as applicable.

20.2.1 Summary Schedule of Visit Assesments for Surgical Bleeding

Table 7
Summary Schedule of Visit Assesments for Surgical Bleeding

Procedures/ Assessments	**Surgical procedure**				**Post-Operative Day 7 Visit (± 1 day)**	**Post-Operative Day 14 Visit (± 2 day)**
	Priming Dose Procedures (12-24 hours prior to surgery)	**Loading Dose Procedures (≤ 3 hours prior to surgery)**	**Intraoperative**	**Postoperative (day 1 → end of perioperative IP treatment)[a]**		
ECG						X
Physical examination[b]	X	X		X	X	X
Adverse events	X	X	X	X	X	X
Laboratories[c]	X	X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X
IP treatment: rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) or rVWF (vonicog alfa) only infusion	X	X as required	X as required	X as required	X as required	X as required
Concomitant medications and non-drug therapy	X	X	X	X	X	X
[redacted]						X
Hemostatic efficacy assessments[e]			X	X	X	X
Blood loss		X estimated	X actual	X	X[f]	X[f]
Treatment days estimate		X				

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Continued

[a)] The assessments will be performed daily until perioperative IP treatment end (potentially multi-visits)
[b)] Physical Examination: within 2 hours prior to IP infusion start
[c)] For laboratory assessments, see Table 9
[d)] Vital signs: within 30 minutes before infusion start and 30 ± 15 minutes post-infusion
[e)] Completed immediately postsurgery by the operating surgeon 24 hours post last IP infusion or at Day 14 visit (whichever occurs first) by the investigator
[f)] In case bleeding still ongoing

20.3 Clinical Laboratory Assessments

Table 8a
Clinical Laboratory Assessments for On-demand Subject

Procedures/ Assessments	Screening Visit	Baseline Visit (PK-assessment visit)			Prophylaxis Initiation Visit[k]	Interval/Follow-Up Study Visits					PK Assessment[m] at Study Completion			Termination Visit
		Pre-infusion	Infusion	Post-infusion		1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion	Infusion	Post-infusion	Conducted at the 96 hour postinfusion PK Assessment
											12-15[n] month± 2 weeks			
Hematology [a]	X	X		X	X	X	X	X	X	X	X		X	X
Clinical Chemistry[b]	X	X		X	X	X	X	X	X	X	X		X	X
Coagulation Panel/ PK assessment[c]	X	X		X	X	X	X	X	X	X	X		X	
Immunogenicity[d]	X	X			X[l]	X	X	X	X	X	X			X
Viral Serology[e]	X													
Urinalysis[f]	X													
VWD Gene Mutational Analysis / HLA genotype analysis and Analysis of VWF multimers[g]	X													
sP-selectin and D-dimer	X[h]													
Blood Group[i]	X													
Pregnancy Test[j]	X													

[a)] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. Hematology assessments during PK assessments will be determined prior to IP infusion and 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours thereafter. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

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[b)] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin. Clinical chemistry will be determined prior to IP infusion and after 24 ± 2 h, 48 ± 2 hours and 72 ± 2 hours during the PK assessments. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

[c)] Coagulation panel/PK assessment (also refers to IR pre/post dose assessments at prophy initiation visit and each follow-up visit): PT, INR and aPTT (only for screening), VWF:RCo, VWF:Ag, VWF:CB, FVIII:C,; during the PK assessment at the baseline visit blood samples will be drawn 30 min prior PK infusion; once the PK infusion is completed 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 and VWF:RCo, VWF:CB, VWF:Ag, FVIII:C will be determined; for follow-up visits, IR samples will be drawn within 30 minutes pre-infusion and 30 ± 5 minutes post-infusion. During screening and in case of thromboembolic event VWF multimers and ADAMTS13 will be analyzed to judge on a possibly relatedness to UHMW fractions of the IP.

[d)] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII –Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG . In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined. For on-demand subjects, a washout period of at least 72 hours after the last IP infusion is required before blood samples for immunogenicity assessments can be drawn.

[e)] Viral Serology 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; HIV-1/HIV-2 Antibodies

[f)] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH

[g)] Not required if available in the subject's medical history; VWF multimers: additionally in case of thromboembolic events

[h)] At screening and in case of thromboembolic events

[i)] Blood group assessment major blood group (local laboratory) only if not available in the subject's medical history

[j)] Serum pregnancy test (in females of child-bearing potential if no urine sample is available)

[k)] The last post-infusion laboratory assessments coincidence with the initiation visit for prophylactic treatment. After the blood samples are drawn for laboratory assessment for the 96 h post infusion PK assessment, the subject receives the first IP infusion for prophylactic treatment (prophylactic treatment initiation visit).

[l)] Only needed for subjects without PK assessment prior to their first IP infusion in this study.

[m)] A steady state full PK analysis will be performed at the end of the study. 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), the 96 hr sampling can be omitted if not allowed by the dosinig interval.

[n)] Study treatment period is extended by 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. In this case, 12 month ± 2 weeks visit is to be considered as a follow-up visit, and EOS visit is to be performed once the subject can rollover into the continuation study, from 12 month ± 2 weeks to 15 month ± 2 weeks post prophylaxis initiation visit, as applicable.

Table 8b
Clinical Laboratory Assessments for pdVWF Switch Subject

Procedures/ Assessments	Screening Visit	Prophylaxis Initiation Visit	PK Assessment[k] (at prophylaxis dose #5-6)			Interval/Follow-Up Study Visits					PK Assessment[k] at Study Completion			Termination Visit
			Pre-infusion	Infusion	Post-infusion	1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion	Infusion	Post-infusion	Conducted at the 96 hour postinfusion PK Assessment
											12-15[l] month± 2 weeks			
Hematology [a]	X	X	X		X	X	X	X	X	X	X		X	X
Clinical Chemistry[b]	X	X	X		X	X	X	X	X	X	X		X	X
Coagulation Panel/PK assessment[c]	X	X	X		X	X	X	X	X	X	X		X	
Immunogenicity[d]	X	X				X	X	X	X	X	X			X
Viral Serology[e]	X													
Urinalysis[f]	X													
VWD Gene Mutational Analysis / HLA genotype analysis and Analysis of VWF multimers[g]	X													
sP-selectin and D-dimer	X[h]													
Blood Group[i]	X													
Pregnancy Test[j]	X													

Continued on next page

Continued

[a] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. Hematology assessments during PK assessments will be determined prior to IP infusion and 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours thereafter. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

[b] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin. Clinical chemistry will be determined prior to IP infusion and after 24 ± 2 h, 48 ± 2 hours and 72 ± 2 hours during the PK assessments. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

[c] Coagulation panel/PK assessment (also refers to IR pre/post dose assessments at prophy initiation visit and each follow-up visit): PT, INR and aPTT (only for screening), VWF:RCo, VWF:Ag, VWF:CB, FVIII:C,; during the PK assessment blood samples will be drawn 30 min prior PK infusion; once the PK infusion is completed 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 and VWF:RCo, VWF:CB, VWF:Ag, FVIII:C will be determined; for follow-up visits, IR samples will be drawn within 30 minutes pre-infusion and 30 ± 5 minutes post-infusion. During screening and in case of thromboembolic event VWF multimers and ADAMTS13 will be analyzed to judge on a possibly relatedness to UHMW fractions of the IP.

[d] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII –Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG. In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined. For switch subjects, the wash out period may be reduced to the time interval between their pdVWF prophy infusions.

[e] Viral Serology 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; HIV-1/HIV-2 Antibodies

[f] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH

[g] Not required if available in the subject's medical history; VWF multimers: additionally in case of thromboembolic events

[h] At screening and in case of thromboembolic events

[i] Blood group assessment major blood group (local laboratory) only if not available in the subject's medical history

[j] Serum pregnancy test (in females of child-bearing potential if no urine sample is available)

[k] A full steady state PK analysis will be performed. 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) , the 96 hr sampling can be omitted if not allowed by the dosinig interval.

[l] Study treatment period is extended by 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. In this case, 12 month ± 2 weeks visit is to be considered as a follow-up visit, and EOS visit is to be performed once the subject can rollover into the continuation study, from 12 month ± 2 weeks to 15 month ± 2 weeks post prophylaxis initiation visit, as applicable.

20.3.1 Laboratory Sampling for Surgical Bleeding

Table 9
Laboratory Sampling[a] for Surgical Bleeding

Procedures/ Assessments	**Surgical procedure**				**Post-Operative Day 7 Visit (± 1 day)**	**Post-Operative Day 14 Visit (± 2 day)**
	Priming Dose Procedures (12-24 hours prior to surgery)	**Loading Dose Procedures (≤ 3 hours prior to surgery)**	**Intraoperative**	**Postoperative (day 1 → end of perioperative IP treatment)[b]**		
Hematology[c]	X (w/o Differential)	X[d] (w/o Differential)		X (w/o Differential)	X	X
Clinical Chemistry[e]	X	X[d]			X	X
Coagulation panel[f]	X	X	X	X	X	X
VWF inhibitory and binding antibodies, antibodies to other proteins[g]	X	X	X if excessive or unexplainedbleeding	X	X	X
Urinalysis[h]					X	X
VWF Multimers[i]						
Anti VWF IgE antibody testing only in case of allergic reaction/ anaphylaxis						

Continued on next page

Continued

[a)] Blood draws are within 3 hrs prior to infusion start, expect that for the priming dose blood draw is within 30 minutes prior to infusion start. For coagulation panel, an additional 30 ± 5 minutes post-infusion blood draw is needed.
[b)] The assessments will be performed daily until perioperative IP treatment end (potentially multi-visits)
[c)] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.
[d)] Not required if sample already drawn at the time of the priming dose
[e)] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin.
[f)] Coagulation panel: VWF:RCo, VWF:Ag, FVIII:C PT INR and aPTT; in additiona to pre-infusion, 30 ± 5 minutes post infusion blood draw is needed.
[g)] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII – Neutralizing and Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG. In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined.
[h)] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH
[i)] VWD multimers and ADAMTS13 during the study only in case of thrombotic events

20.4 Contraceptive Methods for Female Subjects of Childbearing Potential

In this study, subjects who are women of childbearing potential must agree to utilize a highly effective contraceptive measure throughout the course of the study and for 30 days after the last administration ofIP. In accordance with the Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials (version 2014-09-15)[ii], birth control methods which may be considered as highly effective include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable[iii]
- Intrauterine device (IUD)[iii]
- Intrauterine hormone-releasing system (IUS) [iii]
- Bilateral tubal occlusion[iii]
- Vasectomised partner(s)[iii]
- Sexual abstinence during the entire study period

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

[ii] Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf.

[iii] Contraception methods that are considered to have low user dependency.

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19. [redacted]

20. [redacted]

21. [redacted]

22. SUMMARY OF CHANGES

Protocol 071301: Local Amendment 10 (United States): 2018 SEP 13

Replaces: Global Amendment 6: 2018 MAR 12

In this section, changes from the previous version of the Protocol, dated 2018 MAR 12, are described and their rationale is given.

1. **Throughout the document**
   Description of Change:
   Minor grammatical and/or administrative changes and/or rewording have been made.
   Purpose for Change: To improve the readability and/or clarity of the protocol.

2. **Synopsis (Study Design), Section 8.1**
   Description of Change:
   Added the wording about the possible up-to 3 months' extension of study participation for certain subjects.
   Purpose for Change: To add information about possible extension of study participation for certain subjects.

3. **Synopsis (Planned Duration of Subject Participation), Section 8.**2
   Description of Change:
   Added the note about the possible up-to 3 months' extension of study participation for certain subjects, and clarify that the planned duration of subject participation can therefore be extended to 18 months.
   Purpose for Change: To add information about possible extension of study participation for certain subjects.

4. **Synopsis (Secondary outcome measures), Section 8.3.2.1**
   Description of Change:
   Original text:
   Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 bleeding episodes during the 12-month prophylactic treatment with rVWF (vonicog alfa)
   New text:
   Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 bleeding episodes during the prophylactic treatment with rVWF (vonicog alfa)
   Purpose for Change: To remove the exact prophylactic treatment period as it can be extended beyond 12 month for certain subjects.

5. **Section 6.1**

Description of Change:
Updates were added to reflect the marketing authorization for Vonvendi in US and EU.
Purpose for Change: To provide updated marketing authorization for Vonvendi.

6. **Section 10.3.7**

Description of Change:
The detailed schedules of follow-up visits were removed as for certain subjects 12-month follow-up visit will be scheduled with the need of participation extension.
Purpose for Change: To remove the details to avoid confusion of possible 12-month follow-up visit.

7. **Section 10.3.9**

Description of Change:
End of study visit time was removed as for certain subjects the EOS visit can occur after 12 months with the need of participation extension.
Added the note about the possible up-to 3 months' extension of study participation for certain subjects
Purpose for Change: To add information about possible extension of study participation for certain subjects and to remove the details to avoid confusion of possible delayed EOS visit.

8. **Section 11.6, Section 12.10.2**

Description of Change:
Added the note about the possible up-to 3 months' extension of study participation for certain subjects.
Purpose for Change: To add information about possible extension of study participation for certain subjects.

9. **Section 20.2 Table 6a 6b, Section 20.3 Table 8a 8b**

Description of Change:
Added the footnote to reflect the possible up-to 3 months' extension of study participation for certain subjects.
Purpose for Change: To add note about possible extension of study participation for certain subjects.

10. **Section 20.2 Table 6a 6b, Section 20.3 Table 8a 8b**
Description of Change:
Some clarifications were made to the tables and the footnotes, to reflect the possible up-to 3 months' extension of study participation for certain subjects.
Purpose for Change: To add information about possible extension of study participation for certain subjects.

INVESTIGATOR ACKNOWLEDGEMENT

RECOMBINANT VON WILLEBRAND FACTOR (rVWF)

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

CLINICAL TRIAL PHASE 3

LOCAL AMENDMENT 10 (UNITED STATES): 2018 SEP 13

Replaces: GLOBAL AMENDMENT 6: 2018 MAR 12

OTHER PROTOCOL ID(s)
NCT Number: NCT02973087
EudraCT Number: 2016-001478-14
IND NUMBER: 013657

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT

RECOMBINANT VON WILLEBRAND FACTOR (rVWF)

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

CLINICAL TRIAL PHASE 3

LOCAL AMENDMENT 10 (UNITED STATES): 2018 SEP 13

Replaces: GLOBAL AMENDMENT 6: 2018 MAR 12

OTHER PROTOCOL ID(s)
NCT Number: NCT02973087
EudraCT Number: 2016-001478-14
IND NUMBER: 013657

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
[redacted], MD
[redacted]
Global Clinical Development Operations
Baxalta Innovations GmbH

CLINICAL STUDY PROTOCOL

PRODUCT: Recombinant Von Willebrand Factor (rVWF, vonicog alfa)

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 SHORT TITLE: rVWF IN PROPHYLAXIS

PROTOCOL IDENTIFIER: 071301

CLINICAL TRIAL PHASE 3

LOCAL AMENDMENT 11 (RUSSIA): 2019 JAN 28

Replaces:
AMENDMENT 6: 2018 MAR 12

ALL VERSIONS:
Local (Russia) Amendment 11: 2019 JAN 28
Local (United States) Amendment 10: 2018 SEP 13
Local (Turkey) Amendment 9: 2018 SEP 13
Local (Czech Republic) Amendment 8: 2018 MAY 18
Local (Germany) Amendment 7: 2018 MAY 18
Amendment 6: 2018 MAR 12
Local (Czech) Amendment 5: 2017 AUG 08
Local (Germany) Amendment 4: 2017 AUG 04
Amendment 3: 2017 AUG 03
Amendment 2: 2016 DEC 15
Amendment 1: 2016 APR 08
Original: 2014 FEB 09

OTHER ID(s)
NCT Number: NCT02973087
EudraCT Number: 2016-001478-14
IND NUMBER: 013657

Study Sponsor(s):

Baxalta US Inc.
300 Shire Way
Lexington, MA 02421, US

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna, AUSTRIA

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted]
Global Clinical Development Operations
Baxalta Innovations GmbH

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (e.g. investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) and suspected unexpected serious adverse events (SUSARs) to the ECs.

ALL SAEs, INCLUDING SUSARs, ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT.

Bleeding events that meet seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) should be reported on the SAE eCRF and SAE Report form as an SAE.

Drug Safety contact information:

Baxalta Global Drug Safety fax number: [redacted]

OR

email: [redacted]

For definitions and information on the assessment of these events, refer to the following:

- Adverse Events (AEs), Section 12.1
- SAEs, Section 12.1.1.1
- SUSARs, Section 12.1.1.2
- Assessment of AEs, Section 12.1.2
- Safety Reporting, Section 12.1.2.3

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	Recombinant von Willebrand factor (rVWF, vonicog alpha)
Name(s) of Active Ingredient(s)	Recombinant von Willebrand factor (rVWF, vonicog alpha)
CLINICAL CONDITION(S)/INDICATION(S)	
Subjects with severe von Willebrand disease (VWD) (baseline VWF: Ristocetin cofactor activity (VWF:RCo) <20 IU/dL) requiring prophylactic treatment with coagulation factor replacement	
PROTOCOL ID	071301
PROTOCOL TITLE	A prospective, phase 3, open-label, international multicenter study on efficacy and safety of prophylaxis with rVWF in severe von Willebrand disease
Short Title	rVWF in prophylaxis
STUDY PHASE	Phase 3
PLANNED STUDY PERIOD	
Initiation	2017 OCT
Primary Completion	2019 Q4
Study Completion	2019 Q4
Duration	27 months
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
The purpose of this phase 3 study is to investigate the efficacy and safety, including immunogenicity, thrombogenicity and hypersensitivity reactions, as well as pharmacokinetics (PK), [redacted] and [redacted] of prophylactic treatment with rVWF (vonicog alfa) in adult subjects with severe VWD.	
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.	
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 FVIII activity	

Exploratory Objectives	
[redacted]	
STUDY DESIGN	
Study Type/ Classification/ Discipline	Efficacy and Safety
Control Type	No control
Study Indication Type	Prophylaxis and treatment of bleeding episodes
Intervention model	Single-group
Blinding/Masking	Open-label
Study Design	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, [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 (pdVWF switch subjects) will receive prophylactic treatment with rVWF (vonicog alfa) for a 12-month period (up to 15 months for the qualified subjects to rollover into the continuation study, if the continuation study start up is delayed beyond the completion of subject's 12-month visit).
Planned Duration of Subject Participation	Approximately 15 to 18* months * Study treatment period is extended by 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.
Primary Outcome Measure	
Efficacy • Annualized bleeding rate (ABR) for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa)	

Secondary Outcome Measures

Additional efficacy of prophylactic treatment with rVWF (vonicog alfa)

- ABR percent reduction success for OD subjects defined as at least 25% reduction of ABR for spontaneous (not related to trauma) bleeding episodes during rVWF (vonicog alfa) prophylaxis relative to the subject's own historical ABR during on-demand treatment
- ABR preservation success for pdVWF switch subjects 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 during prophylactic treatment with pdVWF
- Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 bleeding episodes during the 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
- Spontaneous ABR 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)

Safety

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

Pharmacokinetics (PK) and Pharmacodynamics (PD)

- PK parameters after a washout for on-demand 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 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 VWF:RCo, Von Willebrand factor antigen (VWF:Ag), Von Willebrand collagen binding activity (VWF:CB).
- PD parameters after a washout for on-demand subjects: C_{max}, T_{max}, and $AUC_{0-tlast}$ as measured in FVIII activity by the 1-stage clotting assay (FVIII:C).
- PK parameters at steady state for on-demand and switch subjects: area under the concentration versus time curve from 0 to end of the partial dosing interval ($AUC_{0-tau;ss}$), 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. PK parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.

- PD parameters at steady state for on-demand 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 (FVIII:C). PD parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.
- Time course of FVIII clotting activity (FVIII:C) levels.

Exploratory Outcome Measures

[redacted]

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**Dosage form**: powder and solvent for solution for injection **Dosage frequency**: <u>Prophylactic Treatment</u> Subjects transitioning from on-demand treatment will receive twice weekly infusion with rVWF (vonicog alfa) at doses of 50 ± 10 IU/kg rVWF:RCo. Dosage may be individualized within this range based on: • available historical PK data • type and severity of bleeding episodes the subject has experienced in the past • monitoring of appropriate clinical and laboratory measures The starting dose can, after consultation with the Sponsor, be increased up to 80 U/kg if considered necessary to assure effective prophylaxis. Subjects switching from pdVWF prophylaxis treatment: the weekly dose (IU/kg) of rVWF (vonicog alfa) for each patient will be equivalent (± 10%) to the weekly VWF dose received during prophylactic treatment with pdVWF. The weekly dose should be divided into 2 infusions, 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. A once weekly dose regimen will be allowed after switch to rVWF (vonicog alfa) if the patient has been on a once weekly dose regimen with pdVWF. Dose and dose interval may, after consultation with the sponsor, be further individualized based on: • available historical PK data • type and severity of bleeding episodes the subject has experienced in the past • monitoring of appropriate clinical and laboratory measures <u>Treatment of Bleeding Episodes:</u> Dosage must be individualized based on the subject's weight, type and severity of bleeding episode and monitoring of appropriate clinical and laboratory measures. In general, an initial dose of 40-60 IU/kg VWF:RCo with or without 30-45 IU rFVIII [ADVATE, octocog alfa]/kg is recommended (rVWF:rFVIII ratio of 1.3:1: ± 0.2). In cases of major bleeding episodes, a dose of up to 80 IU/kg VWF:RCo may be infused. Subsequent doses, if necessary, will be administered with or without ADVATE (rFVIII, octocog alfa) to maintain VWF:RCo and FVIII levels for as long as deemed necessary by the investigator. **Mode of Administration:** intravenous

SUBJECT SELECTION	
Targeted Accrual	Approximately 22 adult subjects with severe VWD will be included to have ≥8 subjects in each cohort (OD and switch). A total of at least 5 type 3 VWD subjects will be followed for 12 months.
Number of Groups/ Arms/ Cohorts	Single-group

Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding:
    a. Type 1 (VWF:RCo <20 IU/dL) or,
    b. Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2M or,
    c. Type 3 (VWF:Ag ≤3 IU/dL).
2. Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.
3. For on-demand patient group, subject currently receiving on-demand treatment for whom prophylactic treatment is recommended by the investigator.
4. For pdVWF switch patient group, subject has been receiving prophylactic treatment of pdVWF products for no less than 12 months prior to screening.
5. For on-demand patient group, subject has ≥3 documented spontaneous bleeds (not including menorrhagia) requiring VWF treatment during the past 12 months.
6. Availability of records to reliably evaluate type, frequency and treatment of bleeding episodes during at least 12 months preceding enrollment. Up to 24 months of retrospective data should be collected if available. Availability of dosing and factor consumption during 12 months (up to 24 months) of treatment prior to enrollment is required for pdVWF switch subjects and is desired (but not a requirement) for on-demand subjects.
7. Subject is ≥18 years old at the time of screening and has a body mass index ≥15 but <40 kg/m^2.
8. If female of childbearing potential, subject presents with a negative blood/urine pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.
9. Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

Subjects who meet ANY of the following criteria are not eligible for this study:

1. The subject has been diagnosed with Type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD (e.g., qualitative and quantitative platelet disorders or elevated prothrombin time (PT)/international normalized ratio [INR] >1.4).
2. The subject is currently receiving prophylactic treatment with more than 5 infusions per week.
3. The subject is currently receiving prophylactic treatment with a weekly dose exceeding 240 IU/kg.
4. The subject has a history or presence of a VWF inhibitor at screening.

5. The subject has a history or presence of a FVIII inhibitor with a titer ≥0.4 Bethesda units (BU) (by Nijmegen modified Bethesda assay) or ≥0.6 BU (by Bethesda assay).
6. The subject has a known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins.
7. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
8. The subject has a medical history of a thromboembolic event.
9. The subject is human immunodeficiency virus (HIV) positive with an absolute Helper T cell (CD4) count <200/mm^3.
10. The subject has been diagnosed with significant liver disease per investigator's medical assessment of the subject's current condition or medical history or as evidenced by any of the following: serum alanine aminotransferase (ALT) greater than 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).
11. The subject has been diagnosed with renal disease, with a serum creatinine (CR) level ≥2.5 mg/dL.
12. The subject has a platelet count <100,000/mL at screening.
13. The subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to signing the informed consent.
14. The subject is pregnant or lactating at the time of enrollment.
15. Patient has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
16. The subject has participated in another clinical study involving another investigational product (IP) or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
17. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
18. The subject is scheduled for a surgical intervention.
19. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
20. The subject has a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
21. The subject is in prison or compulsory detention by regulatory and/or juridical order
22. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.

Delay criteria

1. If the subject presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) the screening visit will be postponed until the subject has recovered.

STATISTICAL ANALYSIS

Sample Size Calculation

Approximately 22 adult subjects with severe VWD will be included in the study. The aim is to have ≥8 subjects in each cohort (OD and switch). A total of at least five type 3 VWD subjects will be followed for 12 months. 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).[1]

Planned Statistical Analysis

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

The Safety Analysis Set will be composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

The Per-Protocol (PP) Analysis Set will be composed of subjects who are at least 70% compliant regarding the number of scheduled prophylactic infusions. Only subjects who meet all study entry criteria and who have no major protocol violations that might impact primary efficacy assessments will be included in the PP analysis set.

The Pharmacokinetic Full Analysis Set (PKFAS) will be composed of all subjects who received the PK infusion and who provided acceptable data for PK and PD analysis. Acceptable PK/PD data will be defined in the Statistical Analysis Plan.

Primary Outcome Measure:

No formal statistical hypothesis test is planned for the analysis. Spontaneous ABR while treated with rVWF (vonicog alfa) for each cohort, on demand and switch subjects, will be estimated using a negative binomial regression. The prior ABR for each cohort will be based on historical data collected from each enrolled subject. The two ABRs (observed on the study and historical) will be assessed 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 ABR ratio together with a two-sided, 95% confidence interval (CI) will be reported for each cohort.

The difference in on-study ABR relative to historical ABR will be summarized descriptively.

The primary efficacy analysis will be based on the FAS and will be summarized by the two cohorts: on-demand and switch subjects. As a supportive analysis, the same analysis will also be carried out on the per-PP analysis set.

Secondary Outcome Measures:

In general, data for secondary efficacy analysis will be summarized by the two cohorts: on-demand and switch subjects and when applicable overall. Mean, standard deviation, median, range, quartiles will be calculated for continuous endpoints. Proportions will be calculated for categorical endpoints. Confidence intervals at the 95% level will be provided when appropriate.

Additional efficacy of prophylactic treatment with rVWF (vonicog alfa):

The number and proportion of on-demand subjects with ABR percent reduction success (i.e. ≥ 25%) will be calculated together with a two-sided 95% CI for the proportion.

The number and proportion of pdVWF switch subjects with ABR preservation success will be reported together with the corresponding 95% two-sided CIs for the proportion.

The number and proportion of subjects with categorized spontaneous ABR (i.e. 0, 1-2, 3-5, more than 5 bleeds) will be reported descriptively.

Summary statistics for the total number of infusions, as well as average number of infusions per week will be provided. The total weight adjusted consumption of rVWF (vonicog alfa) during prophylactic treatment will be provided. If applicable, historical data on consumption of pdVWF prior to the study will be summarized as well.

The change in spontaneous ABR from the historical rate to that during the rVWF (vonicog alfa) prophylaxis period will be summarized by location of bleeding (GI, epistaxis, joint bleeding, menorrhagia, oral and other mucosa, muscle and soft tissue, etc.).

Pharmacokinetics (PK) and Pharmacodynamics (PD):

The following PK parameters, based on the initial PK assessment after a washout for on-demand subjects, will be listed and summarized descriptively for VWF:RCo, VWF:Ag and VWF:CB: IR, $T_{1/2}$, MRT, $AUC_{0-\infty}$, $AUC_{0\text{-tlast}}$, C_{max}, T_{max}, V_{ss}, and CL. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity (FVIII:C), based on the initial PK assessment after a washout for on-demand subjects will be assessed using C_{max}, T_{max}, and $AUC_{0\text{-tlast}}$. These PD parameters will be listed and summarized descriptively.

PK parameters at steady state ($AUC_{0\text{-tau;ss}}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$) for the partial dosing interval will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study for VWF:RCo, VWF:Ag and VWF:CB and summarized descriptively for subjects with the same dosing regimens. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity (FVIII:C) will be assessed using $AUC_{0\text{-tau;ss}}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$. These PD parameters will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study and will be summarized descriptively for subjects with the same dosing regimens.

For the on-demand subjects, the PK of VWF:RCo will be analyzed using a population PK approach to characterize the single and multiple dose pharmacokinetics, including associated variability, of VWF:RCo in the study population.

For the switch subjects, differences in $AUC_{0\text{-tau;ss}}$, $C_{max;ss}$, and $C_{min;ss}$ assesses shortly after reaching steady state and assessed at the end of the study will be assessed by ratio of geometric means and corresponding two-sided 95% confidence intervals for VWF:RCo, VWF:Ag, VWF:CB, and FVIII:C. 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.

Descriptive statistics will be used to summarize VWF:RCo, VWF:Ag, VWF:CB, and FVIII:C levels for each nominal time point on the PK curve. For all subjects activity/concentration vs. time curves will be prepared.

Safety:

Safety analysis will be performed overall and by the two cohorts: on-demand and switch subjects.

Treatment-emergent AEs (TEAEs) are defined as AEs with start dates on or after the first exposure to IP. Summaries of AEs will be based on TEAEs unless otherwise indicated.

Occurrence of AEs and serious AEs (SAEs) will be summarized descriptively, by system organ class and preferred term. The number and percentage of subjects who experienced AEs and SAEs, and the number of AEs and SAEs will be tabulated. In addition, the number of subjects who experienced AEs assessed as related to IP by the investigator, and the number of IP-related AEs will be tabulated. The number of patients with AEs by severity will be presented similarly.

A listing of all AEs will be presented by subject identifier, age, sex, preferred term and 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.

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 infusion, irrespective of being related or not related to treatment. Temporally associated AEs will be presented in summary tables.

Adverse events of special interest (AESI), such as hypersensitivity reactions and thromboembolic events, will be monitored throughout the study and statistical analysis will be conducted based on the search criteria (eg, standardized MedDRA queries [SMQ]) determined prior to database lock, and summarized.

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.

Clinically significant changes relative to baseline in vital signs and clinical laboratory parameters (hematology, clinical chemistry) will be reported.

4. TABLE OF CONTENTS

Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABR	Annualized bleeding rate
ADAMTS13	A Disintegrin And Metalloproteinase with a Thrombospondin type 1 motif, number 13
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the plasma concentration /time curve from time 0 to infinity
$AUC_{0-tau;ss}$	Area under the plasma concentration /time curve from time 0 to end of the partial dosing interval
$AUC_{0-tlast}$	Area under the plasma concentration /time curve from 0 to the last measurable concentration
aPTT	Activated partial thromboplastin time
B19V	Parvovirus B19
BP	Blood pressure
BU	Bethesda Unit
BUN	Blood urea nitrogen
BW	Body weight
CAM	Cell adhesion molecule
CBC	Complete blood count
CD4	Helper T cell
CHO	Chinese hamster ovary
CI	Confidence interval
Cl	Chloride
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max;ss}$	Maximum plasma concentration during the partial dosing interval at steady state
$C_{min;ss}$	Minimum plasma concentration during the partial dosing interval at steady state
CR	Creatinine
CTA	Clinical Trial Agreement
eCRF	Electronic case report form
DDAVP	Desmopressin acetate
DMC	Data monitoring committee

Abbreviation	Definition
DIC	Disseminated intravascular coagulation
DVT	Deep vein thrombosis
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
[redacted]	[redacted]
FAS	Full analysis set
FVIII	Factor VIII
FVIII:C	Factor VIII clotting activity
GCP	Good Clinical Practice
GI	Gastrointestinal
Glu	Glucose
HAMA	Human anti- mouse antibodies
HAV	Hepatitis A virus
HB	Hepatitis B
HBs	Hepatitis B surface
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
[redacted]	[redacted]
HRP	Horseradish peroxidase
IB	Investigator's brochure
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
INR	International normalized ratio
IP	Investigational product
IR	Incremental recovery

Abbreviation	Definition
i.v.	Intravenous
K	Potassium
k.o.	Knock out
LDH	Lactate Dehydrogenase
Na	Sodium
NMC	Non-medical complaint
NOAEL	No observed adverse effect level
MRI	Magnetic resonance imaging
MRT	Mean residence time
pdVWF	Plasma derived VWF product
pdVWF/FVIII	Plasma derived VWF product containing fractions of FVIII
PBAC	Pictorial Blood Assessment Chart
PCR	Polymerase Chain Reaction
PEF	Peak expiratory flow
PK	Pharmacokinetic
PKFAS	Pharmacokinetic Full Analysis Set
PKPPAS	Pharmacokinetic Per Protocol Analysis Set
PP	Per protocol
PT	Prothrombin time
Q1, Q3	Quartile
rFVIII	Recombinant factor VIII
rVWF	Recombinant von Willebrand factor
RBC	Red blood cell count
SAE	Serious adverse event
SAER	Serious adverse event report
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
[redacted]	[redacted]
SIC	Subject identification code
SMQ	Standardised MedDRA queries
sP-selectin	Soluble P-selectin
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Terminal phase half life
TEAE	Treatment-emergent adverse event

Abbreviation	Definition
TIA	Transient ischemic attack
T_{max}	Minimum time to reach the maximum concentration
$T_{max;ss}$	Minimum time to reach the maximum concentration at steady state
TTP	Thrombotic thrombocytopenic purpura
ULMW	Ultra-large molecular weight
ULN	Upper limit of normal
V_{ss}	Volume of distribution at steady state
[redacted]	[redacted]
VTE	Venous thromboembolism
VWD	von Willebrand disease
VWF	Von Willebrand factor
VWF:Ag	Von Willebrand factor antigen
VWF:CB	Von Willebrand Factor collagen binding
VWF:RCo	Von Willebrand factor: Ristocetin cofactor activity
WBC	White blood cell

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

Baxalta US Inc. (hereafter referred to as Baxalta or sponsor) has developed a human recombinant von Willebrand Factor (rVWF, vonicog alpha), which is co-expressed with recombinant factor VIII (rFVIII) in a Chinese hamster ovary (CHO) cell line and separated during the subsequent downstream process. To address concerns regarding the risk of transmission of blood-borne pathogens that may be introduced by human plasma, no exogenously added raw materials of human or animal origin are employed in the cell culture, purification, or formulation of the final container product. The only proteins present in the final container product other than rVWF (vonicog alfa) are trace quantities of murine immunoglobulin (IgG, from the immunoaffinity purification), host cell (i.e., CHO) protein, rFurin (used to further process rVWF). rVWF (vonicog alfa) is intended for the treatment of von Willebrand disease (VWD).

rVWF (vonicog alfa) has been developed under the Baxalta internal code BAX111 and is used as investigational product (IP) in this study. rVWF (vonicog alfa) may be used with or without ADVATE (rFVIII, octocog alfa) for the treatment of bleeding episodes (see Section 8.6.4.4). See Section 8.6 for further information on the IPs and their usage in this study. A detailed description of rVWF (vonicog alfa) is also provided in the Investigator's Brochure (IB).

rVWF (vonicog alfa) was granted licensure in the United States in December 2015 under the brand name VONVENDI for the on-demand treatment and control of bleeding episodes in adults diagnosed with VWD and it has been available on the market in the US since 09 August 2016. In April 2018, VONVENDI was also granted licensure in the US by the FDA for an additional indication of perioperative management of bleeding in adults (age 18 and older) diagnosed with VWD. On 31st of August 2018, European Commission implemented the decision granting marketing authorization for VEYVONDI (vonicog alfa) for the treatment of haemorrhage and surgical bleeding and for the prevention of surgical bleeding in adults (age 18 and older) diagnosed with VWD, when desmopressin (DDAVP) treatment alone is ineffective or not indicated. VEYVONDI should not be used in the treatment of Haemophilia A. On 4 October 2018, VEYVONDI (vonicog alfa) was granted licensure in Switzerland by Swissmedic for the treatment of haemorrhage or surgical bleeding in VWD, when desmopressin (DDAVP) treatment alone is ineffective or contra-indicated. VEYVONDI should not be used in the treatment of Haemophilia A. On 10 January 2019, VONVENDI was authorized in Canada for the treatment and control of bleeding episodes, and perioperative management of bleeding in adults (age ≥18) diagnosed with VWD.

6.2 Clinical Condition/Indication

Von Willebrand Factor (VWF) is a large multimeric glycoprotein with a molecular weight that varies from 500 to 20,000 kDa. VWF is normally found in plasma and produced in the alpha-granules of platelets and in endothelial cell organelles known as the Weibel-Palade bodies. VWF mediates platelet adhesion and aggregation at sites of vascular injury, one of the key functions in primary hemostasis. VWF also serves to stabilize coagulation factor VIII (FVIII), where FVIII is an essential cofactor of secondary hemostasis, which leads to fibrin clot formation.[2] Qualitative and/or quantitative deficiencies of VWF lead to a highly variable bleeding diathesis known as VWD, the most common of the hereditary coagulation factor deficiencies. Penetrance of VWD is highly variable, with only a small fraction of mildly affected patients displaying clinical symptoms or a family history of a bleeding diathesis.

The current biochemical-based classification distinguishes disorders arising from partial quantitative (type 1), qualitative (type 2), or virtually complete (type 3) deficiencies of VWF. Up to 70% of VWD patients are diagnosed with type 1 VWD, which may also be associated with minor functional defects in the molecule. In general, patients with type 1 VWD display mild clinical symptoms. Approximately 20 to 30% of VWD patients are diagnosed with type 2 VWD. Type 2 VWD is further divided into 4 subtypes (A, B, N, and M), reflecting distinct classes of functional abnormalities. These defects result in abnormal functional and/or multimeric distribution patterns that facilitate their diagnosis. The bleeding diathesis is usually moderate and primarily affects the mucosal tissues. Type 2N VWD patients are sometimes misdiagnosed as mild hemophilia A. Finally, approximately 1% percent of VWD patients exhibit a total or near total absence of VWF, which is classified as type 3 VWD. The incidence of type 3 VWD is estimated at $0.5\text{-}1.0 \times 10^{6}$. This type is also associated with a very low FVIII level (typically <5%) because the VWF carrier function for FVIII is lost. Replacement of VWF alone stabilizes endogenous FVIII, resulting in hemostatic levels within several hours post-infusion. Published results from studies of a plasma-derived VWF (pdVWF) concentrate demonstrated an increase of FVIII at an approximate rate of 5.8 ± 1 IU dL^{-1} h^{-1}.[3] Type 3 VWD patients display severe hemorrhagic symptoms with bleeding predominantly in mucosal tissues, muscle and joints. All VWD patients, particularly those with type 2 or type 3 VWD, are at an increased risk for life-threatening bleeding episodes.

6.3 The Role of Prophylaxis in the Management of VWD

The goals of long term prophylaxis in VWD are to maintain VWF and FVIII at sufficient levels to reduce the frequency and duration of bleeding episodes, the need for red blood cell transfusions, and the risk of complications, such as arthropathy.[4] In contrast to hemophilia, routine prophylaxis is not as established in VWD, although prophylaxis for patients with severe VWD was in use in Sweden already during the 1950s.[5] In those early days of VWD treatment, plasma FVIII concentrates containing VWF fractions were applied for replacement therapy, which then were followed by plasma derived VWF products containing fractions of FVIII (pdVWF/FVIII).

A Swedish cohort including 37 patients with type 3 VWD under prophylactic median treatment of 11 years (range 2 to 45 years) was retrospectively analyzed.[6,7] The doses used for prophylaxis, given once weekly for at least 45 weeks per year, were calculated based on 12 to 50 IU/kg body weight (BW) of FVIII clotting activity (FVIII:C) which approximately corresponded to 24-100 IU/kg von Willebrand factor: Ristocetin cofactor activity (VWF:RCo) considering that mainly Haemate with a known VWF:RCo/FVIII:C ratio of about 2 was used. An escalation of doses from 1 to 3 dose levels was allowed depending on the frequency and severity of bleeding episodes. The results demonstrate that under long-term prophylaxis the number of bleeds could be reduced dramatically. Whereas the median value for bleeds per year was about 10 before prophylaxis this value could be reduced to less than 1 bleed per year during prophylaxis.

The benefit of prophylaxis for such indications was retrospectively also demonstrated in a cohort of Italian patients including type 3, 2A, 2M and type 1 patients. Prophylaxis was started after severe gastrointestinal or joint bleeding episodes and completely prevented bleeding episodes in 8 of these 11 patients and largely reduced the need of blood transfusions in the remaining 3. A regimen of 40 IU rVWF:RCo/kg was applied every other day or twice a week. A prospective study on prophylaxis, the PRO.WILL study, has been initiated in Italy.[8]

The results of a prospective study investigating the prophylaxis in children and young adults showed a significantly reduced bleeding frequency and bleeding score (3 vs. 0.07; 3 vs. 0. $p<0.001$) compared to the pre-prophylaxis values. The median dose was 40 (20-47) IU/kg VWF:RCo administered mainly twice weekly in 23 patients, 3 times a week in 7 patients and 4 times a week in 2 children.[9]

The VWD Prophylaxis Network initiated the VWD International Prophylaxis (VIP) trial to investigate the role of prophylaxis in patients with severe VWD including Type 1, 2, and 3. The dose of the factor replacement product was 50 IU /kgVWF:RCo.

The frequency of the dose depended on the type of bleeding and could be increased from once weekly to twice weekly or 3 times per week. For the treatment of menorrhagia the dose of 50 IU/kg VWF:RCo was given on the first day of menses for 2 cycles. The frequency could be increased to Day 1 and 2 for 2 cycles or to Day 1, 2, and 3 of menses.

The study contains both retrospective and prospective study components. Results from the retrospective study component were published, including 61 subjects on prophylactic regimen in the past 6 months prior to enrollment or subjects with a history of prophylaxis over at least 6 month.[10] Differences in annualized bleeding rates (ABR) within individuals (during prophylaxis – before prophylaxis) were significant for those with primary indications of epistaxis (P = 0.0005), joint bleeding (P = 0.002) and GI bleeding (P = 0.001). The difference in the group whose primary indication for treatment was abnormally heavy bleeding at menstruation (n = 4) was not significant (P = 0.25). The reduction of mucosal bleeding likely not only dependents on normal circulating levels of active VWF, but also on the presence of discrete concentrations of normal VWF inside the platelets and within endothelial matrices. The low subject number (n=4) and the treatment scheme for menorrhagia on Days 1, 2, and 3 of menses which might represent rather on-demand than prophylactic treatment may also account for the outcome in this study.

Results from the prospective study component were reported recently.[11] Eleven subjects completed the study. Six subjects had type 2A, and 5 subjects had type 3 VWD. Six subjects presented with epistaxis, 3 with GI bleeding, and 2 with joint bleeding. Seven subjects had dose escalation above the first level. Among the 10 subjects with evaluable bleeding log data, the use of prophylaxis decreased the median ABR from 25 to 6.1 (95% confidence interval [CI] of the rate difference: -51.6 to -1.7), and the median ABR was even lower (4.0; 95% CI: -57.5 to -5.3) when the subjects reached their final dosing level. The authors concluded that this was the first prospective study to demonstrate that prophylaxis with VWF concentrates is highly effective in reducing mucosal and joint bleeding rates in clinically severe VWD.

The results of the VIP study and previous investigations suggest that VWD patients with recurrent bleeding episodes and severe menorrhagia will benefit from a prophylactic VWF replacement therapy. There is evidence that up to 40% of patients with type 3 VWD experience joint bleeding which can lead to hemophilic arthropathy. Other potential indications for prophylaxis include patients with type 2A or 2B VWD with recurrent gastrointestinal bleeding, menorrhagia or frequent epistaxis.[4] Long-term prophylaxis for most patients with type 3 VWD and in some patients with type 1 or 2 VWD, depending on the pattern of bleeding, may be the treatment option of choice.

Although the main experience with long-term prophylaxis is with secondary prophylaxis, primary prophylaxis starting at young age is recommended to prevent arthropathy in patients with severe VWD.[12]

However, further studies are needed to develop evidence-based guidelines for prophylactic treatment in VWD.

6.4 Populations to be Studied

A total of approximately 22 eligible, adult subjects with severe VWD (baseline VWF:RCo <20 IU/dL) are planned to be enrolled. Two cohorts of patients will be included: patients currently receiving on-demand VWF treatment (OD subjects) and patients currently on prophylactic treatment with pdVWF (pdVWF switch subjects), and the aim is to have ≥8 subjects in each of the 2 cohorts, with a total of at least 5 type 3 VWD subjects followed for 12 months. Enrolled subjects (i.e., subjects who have signed the informed consent form) will be eligible to participate in the study if they meet all of the inclusion criteria (see Section 9.1) and none of the exclusion criteria (see Section 9.2).

6.5 Findings from Nonclinical and Clinical Studies

The following summarizes the key findings from relevant nonclinical studies as well as from the completed clinical studies **070701** (Phase 1 pharmacokinetics [PK] and safety in VWD), **071001** (Phase 3 safety and efficacy in the treatment of bleeding episodes in VWD), **071101** (Phase 3 efficacy and safety in VWD subjects undergo elective surgical procedures), **071104** (Phase 1 safety and PK in hemophilia A), and **071401** (Phase 3, expanded access in a single subject with VWD). Potential risks and efficacy of rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) are summarized in the following sections. For additional information on nonclinical and clinical Phase 1 results refer to the rVWF (vonicog alfa) IB.

6.5.1 Findings from Nonclinical Studies

6.5.1.1 Primary Pharmacodynamics

Efficacy of rVWF (vonicog alfa) combined with ADVATE (rFVIII, octocog alfa) was shown in VWD animal models, which have also low endogenous FVIII levels. Time to occlusion and stable thrombus formation was assessed in the carotid occlusion model in VWD mice. The results demonstrated that rVWF (vonicog alfa) in combination with ADVATE (rFVIII, octocog alfa) acted efficiently in a dose-dependent manner and had higher efficacy than rVWF (vonicog alfa) alone or plasma derived (pd)VWF. These results were confirmed in an additional study assessing blood loss and survival in a tail tip bleeding model in VWD mice. In a VWD dog, rVWF (vonicog alfa) stabilized canine FVIII in the circulation and significantly reduced the bleeding time.

6.5.1.2 Safety Pharmacology

The anaphylactoid and thrombogenic potential of the co-infusion of ADVATE (rFVIII, octocog alfa) and rVWF (vonicog alfa) and the co-infused product's effects on blood pressure, cardiac and respiratory function and parameters of coagulation activation were investigated in 4 in vivo studies in different animal models. Safety pharmacology studies in rats, guinea pigs, rabbits, and dogs revealed no risks for anaphylactoid and thrombogenic potential of ADVATE (rFVIII, octocog alfa) in combination with rVWF (vonicog alfa). All observations in safety pharmacology studies are considered to lie within the biological variability of animal models or occurred due to known species-specific anaphylactoid effects of excipients.

6.5.1.3 Pharmacokinetics

Pharmacokinetic studies of both rVWF (vonicog alfa) alone and combined with human rFVIII (rVWF+ADVATE) were conducted in VWD mice, VWD dogs, VWD pigs, rats, and cynomolgus monkeys. Human rVWF (vonicog alfa) stabilized the endogenous FVIII in VWD mice, VWD pigs, and VWD dogs. Furthermore, the hypotheses that the area under the curve (AUC) with rVWF alone and rVWF+ADVATE is not inferior to the AUC with pdVWF (Haemate P) was tested and confirmed statistically in normal rats. The PK characteristics of ADVATE (rFVIII, octocog alfa) were not affected by co-administration of rVWF (vonicog alfa) in cynomolgus monkeys. The PK data in the FVIII knock out (k.o.) mice model are inconclusive and might not be relevant for the clinical situation. However, a stabilizing effect of VWF on FVIII could be shown in a double k.o. model in a dose dependent manner.

6.5.1.4 Toxicology

Single dose toxicity studies were conducted in C57BL/6J-mice, VWD mice, rats, rabbits, and cynomolgus monkeys. Rats, rabbits, and cynomolgus monkeys showed no signs of toxicity. Signs of microthrombosis, an exaggerated pharmacological effect, were observed in mice. Mice are not capable of sufficiently cleaving the rVWF (vonicog alfa) subunit as murine disintegrin and metalloproteinase with a thrombospondin type 1 motif, number 13 (ADAMTS13) does not decrease the ultra-large molecular weight multimers of rVWF (vonicog alfa).[13] The observed symptoms of microthrombosis are interpreted as a species-specific exaggerated pharmacological effect. Studies evaluating the safety of repeated administration of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) (daily over 14 days) were performed in a rodent (rat) and non-rodent (cynomolgus monkey) species. Reversible signs of exaggerated pharmacological effects (regenerative anemia, thrombocytopenia, and treatment-related histopathologic changes in the heart, liver, and spleen) were observed in rats that were administered 1400 U VWF:RCo/kg /day + 1080 IU ADVATE/kg/day intravenously once daily for 14 days.

Also, these findings are interpreted as a species-specific exaggerated pharmacological effect due to the low susceptibility of human rVWF (vonicog alfa) to cleavage by rodent ADAMTS13.[13] No toxicologically relevant changes were evident for clinical observations, body weight, feed consumption, ophthalmology, urinalysis, coagulation, and serum chemistry parameters, platelet aggregation, and gross pathology. rVWF (vonicog alfa) combined with ADVATE (rFVIII, octocog alfa) was well tolerated in cynomolgus monkeys after daily intravenous (i.v.) (bolus) administration of 100 U VWF:RCo/kg rVWF (vonicog alfa) combined with 77 IU/kg ADVATE (rFVIII, octocog alfa) over a period of 14 days. No adverse effects could be detected in this species. There were no signs of hemolysis, thrombosis, or thrombocytopenia after repeated intravenous application of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa). Therefore, 100 U VWF:RCo/kg/day rVWF (vonicog alfa) with or without 77 IU/kg ADVATE (rFVIII, octocog alfa) was considered the no observed adverse effect level (NOAEL) in this study, which was the highest dose tested. Anti-drug antibodies, however, were formed in both species and resulted in a significant reduction in drug exposure after 14 applications as compared to a single application. These antibodies substantially reduced the systemic exposure to the test substance as compared to a single dose administration. No adverse effects due to antibody formation were observed in both species.

rVWF (vonicog alfa) combined with ADVATE (rFVIII, octocog alfa) was well tolerated locally and no genotoxic potential was evident after 2 in vitro and 1 in vivo genotoxicity study. A study on the influence of co-administration of VWF and ADVATE (rFVIII, octocog alfa) on the immunogenicity of ADVATE (rFVIII, octocog alfa) in 3 different hemophilic mouse models (E17 hemophilic Balb/c mice, E17 hemophilic C57BL/6J mice, and E17 hemophilic human F8 transgenic mice) showed that rVWF (vonicog alfa) does not negatively impact the immunogenicity of ADVATE (rFVIII, octocog alfa) in any of the three different hemophilic mouse models.

6.5.2 Findings from Clinical Studies

The clinical safety, efficacy and PK were assessed in 4 completed trials: one phase 1 study (**070701)**) and two phase 3 studies (**071001** and **071101**) that enrolled patients with VWD; one phase 1 study (**071104**) that enrolled patients with hemophilia A. Details on study design, populations enrolled, and safety and efficacy outcomes of the phase 1 studies are presented in Section 6.5.2.1 and Section 6.5.2.2, the phase 3 study in Section 6.5.2.3, and the phase 3 surgery study in Section 6.5.2.4. Information on a single subject with VWD in Study **071401** is presented in Section 6.5.2.5.

6.5.2.1 Study 070701

Phase 1 clinical study **070701** was a multicenter, controlled, randomized, single-blind, prospective 3-step, dose escalation study to investigate safety, tolerability, and PK of rVWF (vonicog alfa) combined at a fixed ratio with ADVATE (VWF:RCo/FVIII:C of 1.3 ± 0.2:1) in adults with severe VWD.[14] Subjects were enrolled in sequential cohorts in a dose escalating manner: Cohort 1, 2, and 3 received a single intravenous infusion of rVWF:ADVATE at the following doses: 2 IU/kg VWF:RCo (Cohort 1), 7.5 IU/kg VWF:RCo (Cohort 2), and 20 IU/kg VWF:RCo (Cohort 3). Subjects in Cohort 4 received a single intravenous infusion of rVWF:ADVATE and pdVWF/ADVATE at 50 IU/kg VWF:RCo in random order.

The primary endpoint was the tolerability and safety after single dose injections of rVWF:ADVATE at 2, 7.5, 20, and 50 IU/kg VWF:RCo for up to 30 days after the last IP infusion. The data generated in this phase 1 study suggest that rVWF:ADVATE up to the highest investigated dose of 50 IU/kg VWF:RCo is well tolerated and safe in adults with severe VWD. No thrombogenic risk or thrombotic thrombocytopenic purpura (TTP)-like syndrome was observed, and no neutralizing antibodies to VWF or FVIII were identified. There were no deaths or other serious adverse reactions, and no infusions were interrupted or stopped due to an AE. Overall, the reported AE profile was similar between the recombinant and plasma-derived concentrates.

Secondary endpoints were the PK assessment of VWF:RCo, von Willebrand factor antigen (VWF:Ag) and multimeric composition of rVWF (vonicog alfa) as well as FVIII:C at standardized time points after single injections of rVWF:ADVATE and pdVWF:FVIII.

The median VWF:RCo terminal half-life ($T_{1/2}$) of rVWF (vonicog alfa) at the 50 IU/kg dose was 16 hours. $T_{1/2}$ with pdVWF:FVIII at the same dose level appeared shorter at 12.58 hours, however, the limits of the 90% CI were similar (11.73 to 17.7 hours vs. 11.87 to 18.03 hours). The median $T_{1/2}$ of VWF:RCo were shorter with the lower investigated doses: 7.13 hours and 13.23 hours with the 7.5 IU/kg and 20 IU/kg doses, although these data were derived from a much smaller number of subjects.

In consequence of the missing ADAMTS13 cleavage, ultra-large molecular weight (ULMW) multimers are contained in the rVWF (vonicog alfa) final product. The immediate cleavage of these ultra-large multimers by ADAMTS13 upon release into the circulation could be demonstrated applying sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE)/Immunoblot with polyclonal anti-VWF antibodies to detect the resulting rVWF (vonicog alfa) subunit cleavage fragments.

Overall the data generated in this phase 1 study suggest that rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) is well tolerated and safe in adults with severe VWD.

6.5.2.2 Study 071104

This study was a prospective, uncontrolled, non-randomized, multicenter proof of concept study to assess safety and PK of the addition of rVWF (vonicog alfa) to ADVATE (rFVIII, octocog alfa) treatment in 12 evaluable subjects with severe hemophilia A. All subjects underwent 3 PK analyses: the first after infusion with ADVATE (rFVIII, octocog alfa) alone, the second after infusion with ADVATE (rFVIII, octocog alfa) plus 10 IU/kg rVWF (vonicog alfa) and the third after infusion with ADVATE (rFVIII, octocog alfa) plus 50 IU/kg rVWF (vonicog alfa).

The PK analysis was performed at intervals of approximately 8 to 14 days. Before each infusion for PK assessment, there was a wash-out period of at least 5 days and the subjects were not actively bleeding.

Primary outcome measures indicate that co-administration of rVWF (vonicog alfa) slightly sustain ADVATE activity with the highest observed ADVATE (rFVIII, octocog alfa) half-life of 13.74 h (CI 11.44 to 16.52) after co-infusion of 50 IU/kg ADVATE plus 50 IU/kg rVWF:RCo.

The highest improvement in ADVATE (rFVIII, octocog alfa) circulating half-life was observed in subjects with VWF:Ag levels below 100% which indicates an association between baseline VWF:Ag levels and ADVATE (rFVIII, octocog alfa) half-life increase.

No treatment related AEs or SAEs were reported. No subject withdrew due to an AE and there were no deaths. No binding antibodies to VWF, CHO, and rFurin were detectable in the confirmatory assay and no signs of a hypersensitivity to rVWF (vonicog alfa) or ADVATE (rFVIII, octocog alfa) antigen were observed. Laboratory values over time did not indicate any potential safety risk for hemophilia A patients treated with rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) in combination.

In summary, the data indicate that rVWF (vonicog alfa) co-administered with ADVATE (rFVIII, octocog alfa) up to the highest dose of 50 IU/kg VWF:RCo is well tolerated and safe in hemophilia A patients.

6.5.2.3 Study 071001

This was a phase 3, multicenter, open-label, part-randomized clinical study to assess the PK, safety, and efficacy of rVWF:rFVIII and rVWF in the treatment of bleeding episodes in adult subjects with severe type 3 and severe non-type 3 VWD.[15] A total of 49 subjects were enrolled (signed informed consent) and screened, 18 subjects were randomized (randomization only applies to Arm 1[PK50 with treatment of BE] and Arm 2 [PK50 only] see below), 37 subjects were treated with IP (all study arms), and 30 subjects completed the study.

The study consisted of 2 parts (Part A and Part B). Part A consisted of PK assessments alone (Arm 2: PK50 only [without treatment of bleeding episodes]), or PK assessments (Arm 1: PK50 and Arm 3: PK80) plus on-demand treatment period(s) of 6 months for bleeding episodes, or on-demand treatment for bleeding episodes only (Arm 4). Except for subjects in arm 2 who completed study after second PK assessment, subjects receiving treatment for PK assessments and/or bleeding episodes in Part A were to be entered into Part B to continue on-demand treatment for bleeding episodes for 6 additional months for a total of 12 months in the study.

The primary outcome measure was the number of subjects with "treatment success" (extent of control of bleeding episodes), which was defined as a mean efficacy rating score of <2.5 for a subject's IP-treated bleeding episodes during the study. The rate of subjects with treatment success was 100% (Clopper-Pearson exact 90% CI: 84.7 to 100.0) for bleeds where the assessments were made prospectively and excluding GI bleeds. Sensitivity analyses confirmed the results of the primary analysis.

Crossover results at 50 IU/kg VWF:RCo showed that the PK profile for rVWF (vonicog alfa) VWF:RCo was independent of administration alone or with rFVIII (ADVATE, octocog alpha) ($T_{1/2}$: 19.4 hours for rVWF and 16.6 hours for rVWF:rFVIII; IR: 1.8 U/dL per IU/kg infused for both rVWF and rVWF:rFVIII; mean residence time (MRT): 26.7 hours for rVWF and 25.2 hours for rVWF:rFVIII). FVIII levels increased substantially with a median peak at 24 hours of 111.0 U/dL for rVWF:rFVIII and 86.0 U/dL after rVWF alone, indicating that rVWF (vonicog alfa) induces a sustained increase in endogenous FVIII activity. The rVWF (vonicog alfa) PK profile was comparable at 50 IU/kg and 80 IU/kg VWF:RCo, and repeated PK at 80 IU/kg VWF:RCo showed close agreement between pretreatment and end-of-study results.

Further analysis of the PK data from the **071001** study supports the initial use of 50 IU/kg twice weekly for prophylaxis dosing in the present study for those subjects who are moving from on-demand to prophylaxis. Using 50 IU/kg for PK measurements, subjects in the **071001** study exhibiting a $T_{1/2}$ for rVWF of 14, 16, or 19 hours had rVWF plasma concentrations at 72 hours after administration of 2.55, 4.01, and 6.49% above baseline, respectively, and plasma concentrations at 96 hours after administration of 0.78, 1.40, and 2.71% above baseline, respectively. In this context it should be noted that subjects in the present study who have significant spontaneous bleeding while on twice weekly prophylaxis will have their regimen increased to 3 times per week based on clear criteria for different bleeding locations (for details see Section 8.6.4.3.1). Subjects in the present study who are switching from prophylaxis with a pdVWF product will begin on rVWF (vonicog alfa) using their same weekly total dose in IU/kg VWF:RCo used during their pdVWF prophylaxis divided into twice weekly infusions (for details see section 8.6.4.3).

A total of 125 AEs occurred in 25/37 (67.7%) subjects (62/318 infusions [19.5%]) during or after infusion with IP. Of these, 116/125 were non-serious (all mild or moderate; none were severe), and 9 SAEs were reported in 7 subjects. Of 125 total AEs, 38 were temporally associated with IP; 8 AEs were considered causally related to IP: 6 non-serious related AEs (tachycardia, infusion site paraesthesia, electrocardiogram [ECG] t-wave inversion, dysgeusia, generalized pruritis, and hot flush) occurred in 4 subjects, and 2 related SAEs (chest discomfort and increased heart rate) occurred in 1 subject. No deaths occurred during this study.

None of the subjects developed anti-VWF or anti-FVIII neutralizing antibodies and no binding antibodies to VWF or rFurin, or antibodies against CHO protein or anti-Murine IgG were observed. No clinical or subclinical signs or symptoms of a thrombogenic event were observed in this study. Following an initial increase in ultralarge VWF multimers after administration of rVWF (vonicog alfa), a notable decrease in the proportion of large VWF multimers occurred between 12 and 24 hours post infusion, due to degradation by the endogenous ADAMTS13 followed by a continued decline until the end of the 96-hour follow-up period.

Overall, the data support the safe and effective use of rVWF (vonicog alfa) with or without rFVIII (ADVATE, octocog alpha) in the treatment of bleeds in patients with VWD.

6.5.2.4 Study 071101

This was a phase 3, prospective, open-label, multicenter clinical study to evaluate efficacy and safety of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) in elective surgical procedures in adult subjects with severe VWD. A total of 24 subjects were enrolled (signed informed consent) and screened, 15 subjects were treated with rVWF (vonicog alfa), and 15 subjects completed the study.

Eleven subjects underwent a PK assessment by infusion of 50 ± 5 IU/kg rVWF:RCo at an infusion rate of up to 4 mL/min. 12 to 24 hours before surgery, subjects received a dose of 40 to 60 IU/kg rVWF:RCo. Within 3 hours prior to surgery, the subject's FVIII:C levels were assessed with a target of 30 IU/dL for minor and oral surgeries and 60 IU/dL for major surgeries. Within 1 hour prior to surgery, subjects received a dose of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) (depending on the target FVIII:C levels at the 3 hour assessment). VWF and FVIII IR and $T_{1/2}$ for each subject, when known, were used to guide the initial dose and subsequent doses.

The primary outcome measure was the overall assessment of hemostatic efficacy assessed by the investigator (hemophilia physician) 24 hours after last perioperative IP infusion or at completion of day 14 visit, whichever occurred earlier, and was summarized by the percentage of subjects in each efficacy category ("excellent", "good", "moderate" and "none"). Point estimate and corresponding 90% two-sided exact CI was calculated for the rate of subjects with an overall assessment of hemostatic efficacy. All 15 subjects treated with rVWF (vonicog alfa) (with or without ADVATE) for major (10), minor (4), and oral (1) elective surgical procedures had overall hemostatic efficacy ratings of "excellent" or "good". Most (73.3%) subjects had "excellent" overall hemostatic efficacy ratings; of these, 7 underwent major surgery and 4 underwent minor surgery. The remaining 26.7% subjects had "good" overall hemostatic efficacy ratings: 3 underwent major surgery and 1 underwent oral surgery. All 8 subjects with VWD Type 3, the subtype classified as absolute VWF deficiency, had overall hemostatic efficacy ratings of "excellent" (87.5%) or "good" (12.5%).

Intraoperative hemostatic efficacy ratings were also rated as "excellent" or "good" for all 15 treated subjects. Most (86.7%) subjects had "excellent" intraoperative hemostatic efficacy ratings; of these, 8 underwent major surgery, 4 underwent minor surgery, and 1 underwent oral surgery. Two (13.3%) subjects who underwent major surgery had "good" intraoperative hemostatic efficacy ratings. Intraoperative hemostatic efficacy was rated as "excellent" or "good" for all subjects with VWD Type 3: "excellent" for 7 (87.5%) subjects and "good" for 1 (12.5%) subject.

Only 1 subject received an intraoperative dose of rVWF (18.1 IU/kg) and ADVATE (8.1 IU/kg). The median daily postoperative weight-adjusted dose of rVWF (vonicog alfa) (with or without ADVATE) was 23.5 IU/kg on postoperative Day 1 (n=3) and 25.5 IU/kg on postoperative Day 14 (n=2). In subjects treated with rVWF:ADVATE, the daily postoperative weight-adjusted dose was 16.9 IU/kg rVWF and 7.6 IU/kg ADVATE on postoperative Day 1 (n=1) and decreased to 50.8 IU/kg rVWF and 7.6 IU/kg ADVATE on postoperative Day 7 (n=1). For subjects treated with rVWF alone, the median weight-adjusted dose (Q1, Q3) of rVWF was 35.4 IU/kg on postoperative Day 1 (n=2) and decreased to 23.7 IU/kg on postoperative Day 7 (n=4) and 25.5 IU/kg on postoperative Day 14 (n=2).

A total of 11 subjects were evaluated for PK in the study. As expected, postinfusion increases in concentrations of VWF:RCo, VWF:Ac, VWF:Ag, and VWF collagen binding (VWF:CB) were observed. Mean values for VWF:RCo were as follows: AUC0-∞/dose was 37.50 hours*IU/dL per IU/kg infused; AUC0-72h/dose was 34.08 hours*IU/dL per IU/kg infused; T1/2 was 17.83 hours; MRT was 24.32 hours; CL was 0.03117 dL/hour/kg; and volume of distribution at steady state (Vss) was 0.6837 dL/kg. Median values for VWF:RCo were as follows: AUC0-∞/dose was 32.94 hours*IU/dL per IU/kg infused; AUC0-72h/dose was 31.70 hours*IU/dL per IU/kg infused; T1/2 was 14.62 hours; MRT was 21.80 hours; CL was 0.03036 dL/hour/kg; and Vss was 0.7078 dL/kg. The VWF:RCo activity was consistent with that previously observed in clinical studies 071001 and 070701.

rVWF (vonicog alfa) was safe and well tolerated in adults with severe VWD undergoing major, minor, and oral elective surgical procedures. Of the 12 total treatment-emergent AEs (TEAEs) that occurred during the study, 2 deep vein thrombosis events (1 non-serious and 1 serious, as a part of one case) reported in one subject, who underwent total hip replacement surgery and who had concurrent condition of obesity, was assessed by the sponsor as possibly causally-related to study treatment. None of the TEAEs were either a severe allergic or hypersensitivity reaction or developed due to a severe allergic reaction.

One subject with VWD Type 3 who had an intraoperative transfusion of packed red blood cells during total knee replacement surgery tested positive for binding antibodies to VWF on postoperative Day 7 through study completion. No subjects developed neutralizing antibodies to rFVIII or binding antibodies to CHO, rFurin, or murine IgG.

In summary, the data support the safe and effective use of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) in achieving intra- and post-operative hemostasis in adult subjects with severe VWD undergoing major, minor, and oral elective surgical procedures.

6.5.2.5 Study 071401: Single Subject with von Willebrand Disease

One subject who exhibited allergic reactions to currently marketed pdVWF products was treated in the single-subject study **071401** with rVWF (vonicog alfa) only for the bleed treatment of continued hematuria, and for biopsy and surgical resection of a left-kidney mass.

For the initial rVWF (vonicog alfa) infusion, the subject received a test dose of 5% of the total dose of 60 IU/kg rVWF:RCo at an infusion rate of 1 mL/min. After a 10 to 15-minute observation period, no adverse symptoms or signs were noted and the subject received the remaining 95% of the total dose. The subject was monitored for any signs of an allergic reaction, and none were noted. Treatment with rVWF (vonicog alfa) every 12 to 24 hours was to continue at the discretion of the investigator based on VWF levels and clinical symptomatology. The subject had an excellent response and recovery, which allowed for daily dosing of rVWF (vonicog alfa) and, within 24 hours, the subject's bleeding had stopped. Daily dosing of rVWF (vonicog alfa) was maintained and the subject received his last dose on [redacted].

The subject also received rVWF (vonicog alfa) for 7 days for prophylaxis for surgery (surgical resection of a left-kidney mass). The subject experienced no hemorrhagic complications and no AEs that were considered related to the use of rVWF (vonicog alfa).

6.6 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

Current treatment of VWD patients relies on desmopressin and VWF products manufactured from pooled human plasma. Human VWF produced by recombinant technology could offer a new perspective in treatment of VWD. The benefit for the individual subject is anticipated to be significant during this clinical study. He/she may benefit from a product that minimizes excessive FVIII administration and thus allowing individualized dosing of VWF at optimal levels. Variations in VWF multimeric composition may lead to variability with respect to treating or preventing bleeds in VWD subjects, especially mucosal bleeds which are especially problematic. rVWF (vonicog alfa) product manufactured by Baxalta consistently contains ULMW VWF multimers due to the fact that the product has not been exposed to ADAMTS13.

The initial presence of these ULMW VWF multimers, which are subsequently cleaved by the subject's endogenous ADAMTS13, may result in improved platelet and collagen binding and therefore provide more predictable treatment outcomes.

By using a recombinant product, the risk of transmission of adventitious agents and other blood-borne pathogens associated with the use of products of human or animal origin has been eliminated. At this stage of product development, the key societal benefit is a better understanding of advanced treatment options for VWD and enhanced product availability.

These benefits outweigh the following identified or potential risks of rVWF (vonicog alfa):

- allergic-type hypersensitivity reactions as with any intravenous protein product
- the occurrence of thromboembolic events
- the development of neutralizing antibodies to VWF

Refer to the IB for further details on benefits and risks of the IP.

6.7 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996, with Addendum E6(R2) dated Nov 2016 EMA/CHMP/ICH/135/1995), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives 2001/20/EC and 2005/28/EC, the Declaration of Helsinki and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

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

7.2 Primary Objective

The primary objective of this study is to prospectively evaluate the 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.

7.3 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 FVIII activity

7.4 Exploratory Objectives

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

8. STUDY DESIGN

8.1 Overall Study Design

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

Subjects transitioning from on-demand treatment (OD subjects) or subjects switching from prophylactic treatment with pdVWF (pdVWF switch subjects) will receive prophylactic treatment with rVWF (vonicog alfa) for a 12-month period (up to 15 months for the qualified subjects to rollover into the continuation study, if the continuation study start up is delayed beyond the completion of subject's 12-month visit). The dose will be 50 ± 10 IU/kg rVWF twice weekly for OD subjects or will be based on their prior pdVWF dose for pdVWF switch subjects, and 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 Section 8.6.4.3).

The overall duration of prophylactic treatment with rVWF per subject will be at least 12 up to 15* months.

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 Section 8.6.4.4.2).

The overall study design is illustrated in Figure 1.

* Study treatment period is extended by 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.

8.2 Duration of Study Period(s) and Subject Participation

The overall duration of the study is approximately 27 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The subject participation period is approximately 15 to 18* months from enrollment to completion (i.e, last study visit), unless the subject is prematurely discontinued.

* Study treatment period is extended by 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.

8.3 Outcome Measures

8.3.1 Primary Outcome Measure

8.3.1.1 Efficacy

- Annualized bleeding rate (ABR) for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa)

8.3.2 Secondary Outcome Measures

8.3.2.1 Additional efficacy of Prophylactic Treatment with rVWF (vonicog alfa)

- ABR percent reduction success for OD subjects defined as at least 25% reduction of ABR for spontaneous (not related to trauma) bleeding episodes during rVWF (vonicog alfa) prophylaxis relative to the subject's own historical ABR during on-demand treatment
- ABR preservation success for pdVWF switch subjects 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 during prophylactic treatment with pdVWF
- Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 bleeding episodes during the 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
- Spontaneous ABR 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)

8.3.2.2 Safety

- AEs: incidence, severity, causality
- Thromboembolic events
- Hypersensitivity reactions
- Development of neutralizing antibodies to VWF and FVIII
- Development of total binding antibodies to VWF and FVIII

- Development of binding antibodies to CHO proteins, mouse immunoglobulin G (IgG) and rFurin
- Clinically significant changes in vital signs and clinical laboratory parameters relative to baseline

8.3.2.3 Pharmacokinetics (PK) and Pharmacodynamics (PD)

- PK parameters after a washout for on-demand subjects: incremental recovery (IR), $T_{1/2}$, 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 VWF:Rco activity, VWF:Ag, VWF:CB activity.
- PD parameters after a washout for on-demand subjects: C_{max}, T_{max}, and $AUC_{0-tlast}$ as measured in FVIII activity by the 1-stage clotting assay (FVIII:C).
- PK parameters at steady state for on-demand and switch subjects: area under the concentration versus time curve from 0 to end of the partial dosing interval ($AUC_{0-tau;ss}$), 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. PK parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.
- PD parameters at steady state for on-demand and switch subjects: $AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$ as measured in FVIII activity by the 1-stage clotting assay. PD parameters at steady state will be assessed shortly after reaching steady state for switch subjects and at the end of the study for on-demand as well as for switch subjects all based on the longer interval of the irregular dosing intervals employed.
- Time course of FVIII clotting activity (FVIII:C) levels.

8.3.3 Exploratory Outcomes Measures

8.3.3.1 [redacted]

8.3.3.2 [redacted]

8.3.3.3 [redacted]

8.3.3.4 [redacted]

8.4 Randomization and Blinding

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

8.5 Study Stopping Criteria

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 (eg, 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.

The sponsor ultimately 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.

8.6 Investigational Product(s)

8.6.1 Packaging, Labeling, and Storage

8.6.1.1 rVWF (Recombinant von Willebrand Factor, vonicog alfa)

rVWF (vonicog alfa) will be packaged in boxes with 2 glass vials, one containing the rVWF powder, and the second vial containing the diluent (water for injection). Further details are provided in the IB and Pharmacy Manual. The rVWF label will include, at a minimum, the actual VWF:RCo potency and the date of expiration.

rVWF (vonicog alfa) is a powder that should be stored refrigerated (2-8°C [36-46°F]) . Deviations from the storage condition have to be communicated and followed up with the sponsor. Inadequately stored product will have to be placed in quarantine and may only be used after written IP administration authorization by the sponsor. After removal of the product from the refrigerator the product must not be returned to the refrigerator. The reconstituted product has to be used immediately (at least within 3 hours). rVWF (vonicog alfa) must not be used beyond the expiration date printed on the vial label. Avoid freezing at all times.

8.6.1.2 rFVIII (Recombinant Factor VIII, octocog alfa /ADVATE)

ADVATE (rFVIII, octocog alfa) will be packaged in boxes with 2 glass vials, one containing the lyophilized rFVIII, and the second vial containing the diluent. Further details are provided in the IB and Pharmacy Manual. The ADVATE label will include, at a minimum, the actual FVIII:C potency and the date of expiration.

ADVATE (rFVIII, octocog alfa) should be refrigerated (2-8°C [36-46°F]) in powder form and should not be used beyond the expiration date printed on the vial.
Deviations from the storage condition have to be communicated and followed up with the sponsor. Inadequately stored product will have to be placed in quarantine and may only be used after written IP administration authorization by the sponsor. After removal of the product from the refrigerator the product must not be returned to the refrigerator and has to be used immediately. Avoid freezing at all times.

8.6.2 Reconstitution

The reconstitution procedures for both rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) products are detailed in the Pharmacy Manual.

8.6.3 Administration

Following reconstitution, rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) (in case of bleeding episode treatment) should be administered to study subjects at room temperature and within 3 hours of reconstitution. The reconstituted rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa), should be inspected for particulate matter and discoloration prior to administration, whenever the solution and container permit. The solution should be clear and colorless in appearance. If not, do not administer the product. Plastic syringes provided by the sponsor must be used since coagulation factors tend to stick to the surface of glass syringes.

Investigational product infusions should be given at a slow enough rate to ensure the subject's comfort. The rate should not exceed 4 mL/minute The investigator/ subject shall ensure that no visible residual volume remains in the syringe(s) and that the complete content is administered. Upon completion of the infusion, the butterfly catheter should be flushed with at least 2 mL of saline solution. In case of a (central) venous access device, the flush should be with at least 10 mL of saline solution. The IP infusions should be administered over a duration of 2 to 20 minutes, depending on the volume.

Only the actual potencies of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) as stated on the vial labels and described in the Pharmacy Manual should be used.

A variation of up to 10% of the intended dose for prophylactic infusions and of the intended dose for treatment of bleeding episodes is permissible and the exact dose should be recorded on the Case Report Form (CRF). Using of partial vials is not allowed.

At study visits where recovery analysis is being done, vials with the same lot numbers should be used throughout the PK IP infusion per subject.

For treatment of bleeding episodes, sequential administration will be done: separate syringes of the appropriate dose of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) will be prepared for sequential infusion. rVWF (vonicog alfa) should be infused first sequentially followed preferably within 10 minutes by infusion of ADVATE (rFVIII, octocog alfa). Only the actual potencies of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) as stated on the vial labels and described in the Pharmacy Manual should be used.

The final dose of rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) should be at a ratio of 1.3:1 ± 0.2.

8.6.4 Description of Treatment

8.6.4.1 PK-Assessment Treatment

For on-demand subjects, two PK assessments will be performed: an initial PK assessment after a wash-out period and a steady state PK assessments at the end of the study. The IP infusion for the initial PK assessment is scheduled on the baseline visit, which should be within 42 days after the completion of screening procedures and confirmation of eligibility. At the baseline visit the subjects will receive a dose of 50 ± 5 IU/kg rVWF:RCo for PK assessment. 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). A washout period of at least 5 days is required prior to infusion of rVWF (vonicog alpha) for PK assessment. The 2nd PK assessment for on-demand subjects will be performed at steady state at the end of the study(see Section 11.6). Subjects previously enrolled in rVWF studies **070701**, **071001** or **071101** and having previously undergone PK assessments in these studies are required to repeat the PK assessment due to different dose and time points used in these former studies.

For pdVWF switch subjects, two steady state PK assessments will be performed. The 1st PK will be assessed shortly after reaching steady state, which is expected to be 11 days after the 1st prophylactic dose for majority of the subjects, around the prophylactic dose #5-6. The 2nd PK will be at the end of the study. For steady state PK, 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) as long as it won't interfere with subject's the normal dosing schedule, otherwise the 96 hr sampling can be omitted (see Section 11.6). Final sample for PK analysis should be taken before next dose is administered.

8.6.4.2 Prophylaxis Initiation Treatment

The rVWF (vonicog alfa) prophylaxis initiation treatment visit will coincide with the 96 ± 2 h initial PK assessment for on-demand subjects. For pdVWF switch subjects, the rVWF (vonicog alfa) prophylaxis initiation treatment visit should occur within 42 days after the completion of screening procedures and confirmation of eligibility. At this visit subjects will receive their prophylaxis initiation dose. The prophylaxis doses are described in Section 8.6.4.3.

The subject will be trained on IP reconstitution and administration and may then qualify for home treatment (see Section 8.6.4.3.2). Refer to Table 6 (a/b) for study procedures and Table 8(a/b) for clinical laboratory assessments.

8.6.4.3 Prophylaxis Treatment

For on-demand subjects, the standard prophylactic dose is 50 ± 10 IU/kg rVWF:RCo, which may be increased up to 80 IU/kg. All on-demand subjects will initially receive rVWF (vonicog alfa) twice per week (Table 1, Schedule A). Examples of all dosing schedules are provided in Table 1.

For pdVWF switch subjects, the weekly dose (IU/kg) of IP for each patient 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 (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 (Table 1, Schedule B). A once weekly dose regimen will be allowed after switch to rVWF (vonicog alfa) only if the patient has been on a once weekly dose regimen with pdVWF.

Table 1
rVWF (vonicog alfa) Dosing Schedule Examples: Schedules A and B

Example	M	T	W	Th	F	Sat	Sun	M	T	W	Th	F	Sat	Sun
Schedule A	X				X			X				X		
Schedule B	X		X			X		X		X			X	

The prophylaxis dose may be further individualized within the range based on:

- available historical PK data
- type and severity of bleeding episodes the subject has experienced in the past and
- monitoring of appropriate clinical and laboratory measures

The individualized prophylaxic dose assignment will have to be agreed with the sponsor in advance, and the rationale should be well documented.

8.6.4.3.1 Adjustment of Dose or Dose Interval

In general, the dose and/or dose interval for each subject should not be changed unless prompted by clear medical needs. Dose and frequency adjustments should be agreed with the sponsor in advance unless it constitutes an urgent safety measure. The rationale for dosing adjustments needs to be documented in the subject's medical record.

For both OD and switch patients, dose escalations (not exceeding the upper dose limit of 80 IU/kg rVWF:RCo) and increase of dose frequency will only be allowed in case of insufficient therapeutic response with breakthrough bleeding episodes. The criteria for dose and/or frequency escalation are specific to each bleeding indication but, overall, involve 1 significant breakthrough bleeding episode despite the subject being compliant with scheduled prophylaxis treatment. For switch patients who require a dose escalation due to a breakthrough bleed, the frequency should be kept the same but the dose (IU VWF:RCo per infusion) should be increased up to 80 IU VWF:RCo. Following that, increases in frequency may be considered upon consultation with the Sponsor. For on demand subjects who require a dose escalation, at the discretion of the PI upon consultation with the Sponsor, the frequency may be kept the same but the dose (IU VWF:RCo per infusion) should be increased up to 80 IU VWF:RCo. If this proves to be insufficient, then the dosing frequency may be increased in these subjects. Table 2 presents the criteria for dosing escalation per each bleeding indication taken 50 ± 10 IU VWF:RCo/kg twice weekly dose as an example of subject's assigned starting dose.

The criteria are applicable for both OD and switch subjects who were initially assigned to twice weekly dosing. Subjects entering the study will begin prophylaxis treatment according to Schedule A (Table 1) and will remain at this dose and frequency until meeting the criteria for escalation to the next higher schedule: for example, from 2 infusions of 50 ± 10 IU VWF:RCo/kg/week to 3 infusions of 50 ± 10 IU VWF:RCo/kg/week (Schedule B) to achieve an adequate therapeutic response. If a subject started with a weekly dose (possible for switch subjects), similar criteria would apply except that the subject will be excalated to twice weekly dosing if frequency change is necessary.

Table 2
Criteria for Escalation Specific to Each Bleeding Indication

	Schedule A	Schedule B
Joint bleeding	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a spontaneous joint bleeding episode occurs while on this regimen, the subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B following its resolution	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
GI bleeding	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a severe GI bleeding episode, i.e., requiring red blood cell transfusion, occurs while on this regimen, the subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B following its resolution	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Menorrhagia	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) on days 1 and 2 of menses for 2 cycles. Menstrual flow will be monitored by the PBAC score. If the average pictorial chart score is > 185, then the subject will escalate to up to 80 IU/kg or, if necessary, to Schedule B	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) on days 1, 2, and 3 of menses. Menstrual flow will be monitored by the PBAC score.
Epistaxis	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. The subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B in the event of 1 occurrence of breakthrough bleeding requiring intervention such as iron replacement therapy, transfusion, packing, hospitalization; or 2 bleeding events that require treatment with factor replacement	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Oral and Other Mucosa	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. The subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B in the event of 1 occurrence of breakthrough bleeding requiring intervention such as iron replacement therapy, transfusion, packing, hospitalization; or 2 bleeding events that require treatment with factor replacement.	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.
Muscle and Soft Tissue	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) twice per week. In the event a spontaneous bleeding episode occurs while on this schedule, the subject will escalate to up to 80 IU/kg twice per week or, if necessary, to Schedule B following its resolution.	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) 3 times per week.

Abbreviations: GI: gastrointestinal; PBAC: Pictorial Blood Assessment Chart.

If a subject does not adequately respond to rVWF (vonicog alfa) therapy, he/she will be evaluated for the presence of neutralizing and total binding anti-VWF antibodies (see Section 12.9.3.2).

If a subject experiences a bleed while receiving rVWF (vonicog alfa) three times per week, the investigator should treat the bleed with rVWF (vonicog alfa) at doses up to 80 IU VWF:RCo/kg at a frequency determined by the investigator until the bleed resolves. Upon resolution of the bleeding event, the subject will return to their assigned prophylaxis regimen.

It is essential for the success of this study that the subjects adhere to treatment regimens. Therefore, procedures for monitoring subject's compliance are implemented (see Section 10.7).

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. For example, a subject routinely infuses IP on Monday and Thursday, he/she misses the Monday time point and therefore may infuse the IP on the next day (Tuesday) and thereafter proceed with infusing the IP on Thursday (considering a minimum 12 hours between the infusions) and return to the initial schedule.

If more than 30% of infusions of IP are missed within the visit interval of 3 months the subject will be discontinued from the study (see Section 9.4).

8.6.4.3.2 General Instructions for Home Treatment for Prophylaxis

At the discretion of the investigator, a subject may be considered suitable for home treatment only after the subject has received at least 1 infusion of IP in the clinic, either during planned prophylactic IP exposure or during the treatment of bleeding episodes, and meets the following additional criteria:

1. Fully understands the concept of a clinical study and related documentation (documented training of at least 30 minutes),
2. Has a history of previous experience with home treatment including self-administration and treatment with VWF containing concentrates,
3. Has adequate time for initial training of the study drug preparation (preparation, mixing and infusion of the IP(s) (documented training of at least 30 minutes).

This applies both to subjects who were on prior on-demand treatment and to subjects switching form prophylaxis with pdVWF. In the event a healthcare professional is required to administer IP, he/she must be trained and qualified by the investigator on the above procedures prior to the decision for home treatment. A Subject Guideline detailing all instructions and information listed above will be provided to each subject.

8.6.4.4 Treatment of Bleeding Episodes

8.6.4.4.1 General Instructions for Home Treatment of Bleeding Episodes

If a subject experiences a bleeding episode, he/she should contact the study site immediately and the site investigator should provide instructions on the treatment regimen. If the subject initiates the treatment at home, he/she should at least follow up with the study site if a visit is needed as per the standard of care at the center.

In the event a healthcare professional is required to administer treatment at the subject's home, he/she must be trained and qualified by the site investigator on the above procedures prior to the decision for home treatment. Once a subject has received 1 infusion of rVWF (vonicog alfa) in the clinic (either during planned IP exposure or during the treatment of a bleeding episode) and meets the criteria for home treatment, the treatment of bleeding episodes with IP can be conducted at home (see Section 8.6.4.3.2).

If a subject is not qualified for home treatment, rVWF (vonicog alfa) infusions must be administered at the study site.

If a subject experiences a bleeding episode that requires treatment between the screening and the prophylaxis initiation visit, the subject will be treated with IP (rVWF with or without ADVATE). Treatment with IP must occur at the study site unless the subject has previously qualified for home treatment with rVWF (vonicog alfa). If rVWF (vonicog alfa) treatment is not feasible, the subject may use his/her standard of care, such as commercial pdVWF/FVIII products. In any case a washout period of at least 5 days is required prior to rVWF (vonicog alfa) PK infusion at the initial PK assessment visit for on-demand subjects.

If a subject experiences a bleeding episode requiring treatment during the PK assessment, rVWF (vonicog alfa) should be used to treat the bleed. Blood draws for PK assessment will be stopped and the PK assessments will be repeated once the bleed has resolved and the subject is free of any symptoms related with the bleeding episode. Dose and frequency of rVWF (vonicog alfa) infusions or any other replacement therapy to stop the bleed should be recorded in the electronic Case Report Form (eCRF), and the reason for the use of any non-IP product or therapy should be documented.

8.6.4.4.2 Dosing Recommendations for Treatment of Bleeding Episodes

If an acute bleeding episode occurs, the subject will be treated with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa). It is the sponsor's opinion that, in many cases, treatment with ADVATE (rFVIII, octocog alfa) may not be necessary, since rVWF (vonicog alfa) prophylaxis will serve to increase endogenous FVIII levels. However, if endogenous FVIII is below 30-40 % or is unknown and cannot be estimated from the subject's PK study, an infusion of rVWF: ADVATE at an rVWF: ADVATE ratio of 1.3:1± 0.2 should be administered initially. Subsequent infusions should be with rVWF:RCo 40 to 60 IU/kg with or, in many cases, without 30 to 45 IU/kg ADVATE (only to be administered if plasma FVIII levels fall below 30 IU/L during the treatment period). Dosing may be adjusted downward or upward up to 80 IU/kg rVWF at the treating physician's discretion based upon the subject's prior history, PK and other factors.

If FVIII levels are not available, dosing is at the discretion of the investigator based upon the individual subject's PK data. Using ADVATE (rFVIII, octocog alfa) in addition to rVWF (vonicog alfa) in subsequent doses carries the risk of an excessive rise in FVIII:C. Therefore, reduced doses of ADVATE (rFVIII, octocog alfa) and/or prolongation of the dose interval should be considered.

The following is general guidance and the sponsor's suggestion for treatment of breakthrough bleeds, however each PI will determine the treatment based on the local acceptable practice how to monitor and adjust treatment for a bleeding episode. An effort should be made to discuss with the sponsor (or sponsor's delegate) the treatment strategy.

In general the aim of the initial dose should be full replacement of VWF with VWF:RCo levels of >0.6 IU/ml (60%) and FVIII:C of >0.4 IU/mL (40%). In major bleeding episodes, subsequent doses should keep the trough level of VWF:RCo >50% for 3 days and then as deemed necessary by the investigator for subsequent days. In moderate bleeding episodes, the dose and trough level may be reduced to >30% for as long as deemed necessary by the investigator. Treatment for minor bleeding episodes will generally consist of only 1 or 2 doses of rVWF (vonicog alfa) IP.

If the VWF:RCo level is above 150%, a planned treatment should be delayed by at least 12 hours; if the VWF:RCo level is above 200%, a planned treatment should be delayed by at least 24 hours. In either case, a lower subsequent dose (e.g., 20 IU/kg VWF:RCo) may be appropriate.

Dosing recommendations are listed in Table 3.

Dosage must be individualized based on the subject's weight, VWD type, and the severity of the bleeding episode, as well as on monitoring of appropriate clinical and laboratory measures. In the phase 1 study **070701**, 1.0 IU/kg VWF:RCo raised the circulating level of VWF:RCo by 0.017 IU/mL (1.7 %). In the same study, the observed mean half-life for rVWF (vonicog alfa) was 19.3 hours, with a standard deviation of 10.9 hours.

Table 3
rVWF:RCo Dosing Recommendations for the Treatment of Bleeding Episodes Due to VWD

Classification of VWD	Hemorrhage	Dosage (IU VWF:RCo/kg BW)
Type 1 • Severe (Baseline VWF:RCo activity typically <20%)	Minor (e.g., epistaxis, oral bleeding, menorrhagia[a])	40 to 50 IU/kg (1 or 2 doses)
	Major (e.g., severe or refractory epistaxis, menorrhagia*, GI bleeding, CNS trauma, hemarthrosis, or traumatic hemorrhage)	Initial dose 50 to 75 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment
Type 2 (all variants) and Type 3	Minor (clinical indications above)	40 to 50 IU/kg (1 or 2 doses)
	Major (clinical indications above)	Initial dose of 60 to 80 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment

[a] Menorrhagia is defined as excessive bleeding during menstruation. A diagnosis of menorrhagia will be defined by a prospectively completed Pictorial Blood Assessment Chart (PBAC) score >185 and normal cervical cytology or requiring use of a VWF-containing concentrate for treatment of excessive menstrual bleeding for at least one menstrual cycle during the prior year.

Variances of up to 10% in dosing are permissible during treatment of bleeding episodes, but rounding to the nearest vial size should be avoided.

Subjects with non-neutralizing binding anti-VWF antibodies should initially be treated with a dose known to be efficacious based on the subject's medical treatment history which may differ from the recommendations provided in Table 3. Subjects should be monitored for lack of efficacy as well as for FVIII (mandatory), VWF:RCo (mandatory), and VWF:Ag (optional where testing is not available) levels after 3 to 6 hours. Re-dosing with rVWF (vonicog alfa) in combination with ADVATE (rFVIII, octocog alfa) using the same (initial) dose and adaptation of the dosing frequency should be considered until cessation of the bleed, if the FVIII and/or VWF:RCo levels drop below 30%-50% depending on bleeding severity.

The number of subsequent infusions and the dosage levels prescribed will be determined by the investigator on the basis of the clinical severity, response to current therapy, available laboratory data, and the subject's historical treatment for similar bleeding episodes.

8.6.4.5 Treatment of Surgical Bleeding

Subjects enrolled in this study who require surgery or dental procedures will be treated with IP to manage their surgical bleeding then afterwards will resume their prophylactic rVWF (vonicog alfa) treatment schedule. Subjects who at time of screening have an already scheduled surgical intervention are not eligible for participation in the study.

8.6.4.5.1 Major, Minor and Oral Surgery Definition

The following definitions and criteria are used to serve as a guidance for *major, minor and oral surgery*.

Major surgeries generally refer to major orthopedic surgery (e.g., joint replacement, arthroscopic or open synovectomy, arthrodesis, hardware removals like plates or intramedullary nails, etc.), major abdominal surgery (e.g. open or laparoscopic hernioplasty, cholecystectomy, colon or small bowel resection, etc.), major gynecological surgery (e.g. open or laparoscopic myomectomy, hysterectomy, removal of endometriosis, polyps, cysts, adhesiolysis, etc.), major head and neck surgery (e.g.: tonsillectomy, adenoidectomy, rhinoplasty, lymphadenectomy, thyroidectomy, parotidectomy. etc.), any intracranial , cardiovascular or spinal surgery and any other surgery which has a significant risk of large volume blood loss or blood loss into a confined anatomical space. Extraction of impacted third molars is generally also considered major surgery due to the expected difficulty of surgery and the expected blood loss.

Minor surgeries generally refer to interventions such as placement of intravenous access devices, removal of small skin lesions, arthroscopy, gastroscopy, colonoscopy or conisation.

Oral surgeries comprise extractions of fewer than three teeth, if the teeth are non-molars and have no bony involvement.

A summary schedule of visit assessments and laboratory sampling is included in Supplement tables in Section 20.2.1 and Section 20.3.1.

8.6.4.5.2 Preoperative Priming Dose

12- 24 hours prior to surgery, a priming dose with rVWF (vonicog alfa), using the rVWF IR and $T_{1/2}$ for this subject , will be infused to allow the endogenous FVIII levels to raise to at least 30 IU/dL (minor, oral surgery), or 60 IU/dL (major surgery) at the time of the loading dose of rVWF (vonicog alfa) is infused.

As a general guidance a priming dose of 40-60 IU/kg rVWF:RCo will be administered. If not assessed prior to the preoperative priming dose, a IR recovery may be calculated for subjects undergoing minor and oral surgery.

8.6.4.5.3 Preoperative Loading Dose

An rVWF (vonicog alfa) loading dose should be administed within 3 hours before surgery. VWF and FVIII levels should be assessed within 3 hours prior to surgery initiation and results must be available prior to administering the loading dose. If FVIII levels prior to loading dose administration are not at least 30 IU/dL (minor, oral surgery), or 60 IU/dL (major surgery) ADVATE (rFVIII, octocog alfa) will be administered in addition to rVWF (vonicog alfa) in order to raise FVIII:C levels to recommended levels.

The preoperative loading dose will be calculated as the difference in the target peak and baseline plasma VWF:RCo levels divided by the IR (ΔVWF:RCo x BW (kg) /IR). The PK results will be provided prior to the planned surgery. If the IR is not available, assume an IR of 1.7 IU/dL per IU/kg and calculate the initial dose as follows: (100 − baseline plasma VWF:RCo) x BW (kg) / 1.7. For minor and oral surgery, the IR from the Preoperative Priming Dose visit will be used to guide dosing and the target peak is 50-60 IU/dL VWF:RCo and 40-50 IU/dL FVIII. For major surgery, the target peak is 100IU/dL VWF:RCo and 80-100 IU/dL FVIII.

The surgery may only start after normalization of the activated partial thromboplastin time (aPTT).

8.6.4.5.4 Intra- and Postoperative (maintenance) Dosing

After the preoperative loading dose(s), subjects who have not achieved the desired postinfusion recovery will continue to receive rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) as a bolus infusion, depending on VWF and FVIII levels. The peri- and post-operative substitution regimen will be individualized according to the PK results, intensity and duration of the hemostatic challenge, and the institution’s standard of care.

Subjects undergoing minor surgery will be infused with rVWF (vonicog alfa) every 12-24 hours or every other day, targeting ≥30IU/dL (rVWF and FVIII) for at least the first 48 hours.

Subjects undergoing oral surgery will be infused with rVWF (vonicog alfa) at least once within the first 8-12 hours, targeting ≥30 IU/dL (rVWF and FVIII).

Subjects undergoing major surgery will be infused with rVWF (vonicog alfa) every 12-24 hours for at least the first 72 hours post-surgery, targeting a VWF:RCo and FVIII:C trough plasma level >50 IU/dL, followed by further treatment post-72 hours for as long as deemed necessary by the Investigator, targeting a VWF:RCo and FVIII:C trough plasma level of ≥30 IU/dL.

Dose modifications based on pre-infusion VWF/FVIII levels will be performed as needed. For subsequent infusions post surgery, in case pre-infusion levels are not available prior to the consecutive infusion in a timely manner, pre-infusion levels from the previous dose may be used by the investigator for dosing guidance.

Peak plasma level guidance is matching to Section 8.6.4.4.2

A schedule of all perioperative visit assessments and laboratory sampling can be found in supplement tables in Section 20.2.1 and Section 20.3.1.

8.6.4.6 Thrombosis Prophylaxis

Thromboembolic events have been reported in patients who have VWD, especially in the setting of known risk factors for thrombosis including low ADAMTS13 levels. Therefore, subjects who are at risk for developing thromboembolic events should be monitored for early signs of thrombosis, and prophylaxis measures against thromboembolism should be instituted according to current recommendations and standard of care. For all subjects who are VWD patients and are receiving VWF concentrate, attention should be given to avoid exceeding maximal recommended plasma activity levels of VWF:RCo (250 IU/dL) and FVIII (250 IU/dL).

Anticoagulation measures, such as heparin, are acceptable and should follow study site standards. The investigator will record the use and reasons for such measures/agents on the appropriate CRF.

8.6.5 Investigational Product Accountability

The investigator will ensure that the IP(s) is stored as specified in the Pharmacy Manual and that the storage area is secured, with access limited to authorized study personnel. All temperature excursions at the subject's home need to be monitored by the site (please refer to the pharmacy manual). The investigator will maintain records that the IP(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. The IP(s) must be dispensed only at the study site or other suitable location (e.g., infusion center; home, as applicable per study design), as specified in the protocol (see Section 10). Records will be maintained that includes the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

8.7 Source Data

Per ICH E6(R2) on GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). These may be in paper and/or electronic format. Source documents for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

No data will be entered directly onto the CRF.

For additional information on study documentation and CRFs refer to Section 17.2. The use of subject diaries is described in Section 10.5.

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding
   a. Type 1 (VWF:RCo <20 IU/dL) or,
   b. Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2M or,
   c. Type 3 (VWF:Ag ≤3 IU/dL).
5. Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.
6. For on-demand patient group, subject currently receiving on-demand treatment for whom prophylactic treatment is recommended by the investigator.
7. For pdVWF switch patient group, subject has been receiving prophylactic treatment of pdVWF products for no less than 12 months prior to screening.
8. For on-demand patient group, subject has ≥3 documented spontaneous bleeds (not including menorrhagia) requiring VWF treatment during the past 12 months.
9. Availability of records to reliably evaluate type, frequency and treatment of bleeding episodes during at least 12 months preceding enrollment. Up to 24 months retrospective data should be collected if available. Availability of dosing and factor consumption during 12 months (up to 24 months) of treatment prior to enrollment is required for pdVWF switch subjects and is desired (but not a requirement) for on-demand subjects.
10. Subject is ≥18 years old at the time of screening and has a body mass index ≥15 but <40 kg/m^2.
11. If female of childbearing potential, subject presents with a negative blood/urine pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.[i]
12. Subject is willing and able to comply with the requirements of the protocol.

[i] Refer to Section 20.4 for a list of adequate contraceptive methods for females of childbearing potential.

9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

1. The subject has been diagnosed with Type 2N VWD, pseudo VWD, or another hereditary or acquired coagulation disorder other than VWD (eg qualitative and quantitative platelet disorders or prothrombin time (PT)/international normalized ratio [INR] >1.4).
2. The subject is currently receiving prophylactic treatment with more than 5 infusions per week.
3. The subject is currently receiving prophylactic treatment with a weekly dose exceeding 240 IU/kg.
4. The subject has a history or presence of a VWF inhibitor at screening.
5. The subject has a history or presence of a FVIII inhibitor with a titer ≥0.4 Bethesda units (BU) (by Nijmegen modified Bethesda assay) or ≥0.6 BU (by Bethesda assay).
6. The subject has a known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins.
7. The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.
8. The subject has a medical history of a thromboembolic event.
9. The subject is human immunodeficiency virus (HIV) positive with an absolute Helper T cell (CD4) count <200/mm^3.
10. The subject has been diagnosed with significant liver disease per investigator's medical assessment of the subject's current condition or medical history or as evidenced by any of the following: serum alanine aminotransferase (ALT) greater than 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices).
11. The subject has been diagnosed with renal disease, with a serum creatinine (CR) level ≥2.5 mg/dL.
12. The subject has a platelet count <100,000/mL at screening.
13. The subject has been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to signing the informed consent.

14. The subject is pregnant or lactating at the time of enrollment.
15. Patient has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
16. The subject has participated in another clinical study involving another IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
17. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
18. The subject is scheduled for a surgical intervention.
19. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
20. The subject has a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
21. The subject is in prison or compulsory detention by regulatory and/or juridical order.
22. The subject is member of the study team or in a dependent relationship with one of the study team members which includes close relatives (i.e., children, partner/spouse, siblings and parents) as well as employees.

9.3 Delay Criteria

1. If the subject has an acute bleeding episode or presents with an acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) the screening visit will be postponed until the subject has recovered.

9.4 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (i.e., reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the termination visit (including cases of withdrawal or discontinuation) are described in Section 10.6 and Section 20.2.

Discontinuation (i.e., complete withdrawal from study participation) may be due to dropout (i.e., active discontinuation by subject) or loss to follow-up (i.e., discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also will be withdrawn from treatment or discontinued from further study participation for the following reasons:

1. The subject is scheduled for an extended treatment period >3 months with non-topical immunomodulating drugs other than anti-retroviral chemotherapy (e.g., α-interferon, corticosteroid agents [equivalent to hydrocortisone greater than 10 mg/day]) during the course of the study.
2. Subjects with chronic hepatitis B or C develop ALT/AST levels exceeding 5 times the ULN for >1 month.
3. Subjects who experience severe hypersensitivity reactions, e.g., anaphylaxis upon exposure to rVWF (vonicog alfa).
4. Subjects who develop a neutralizing inhibitor to rVWF (vonicog alfa) and/or ADVATE (rFVIII, octocog alfa) (biological assays) that results in significant clinical effect, including but not limited to increasing the weekly dose of rVWF by $\geq$ 50%.
5. Subjects who demonstrate clinical signs of thromboembolic events.
6. The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through completion of the pregnancy and up to 1 year post delivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome.
7. The subject begins lactating. IP exposure will be discontinued. The investigator will record a narrative description of the course of the baby's development.
8. The subject is not compliant with the prophylactic treatment regimen and does not adhere to the frequency of IP administration. Once >30% of infusions are missed within a visit interval (3 months), the subject will be discontinued from further participation in the study.
9. The subject repeatedly uses other VWF products for prophylaxis or for the treatment of bleeding episodes in the absence of an acceptable justification to the sponsor.

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient who provides informed consent (i.e., signs and dates the informed consent form) is considered a subject enrolled in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (e.g., 071301) to be provided by the sponsor, 2- or 3-digit number study site number (e.g., 02) to be provided by the sponsor, and 3- or 4-digit subject number (e.g., 0003) reflecting the order of enrollment (i.e., signing the informed consent form). For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 071301-020003. All study documents (e.g., CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The study site is responsible for maintaining a screening log that includes all subjects who provided informed consent. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRF, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

The overall study design is illustrated in the Figure 1. Details on the procedures to be performed at each study visit, including screening, are provided in Supplement 20.2 „Schedule of Study Procedures and Assessments“ and Supplement 20.3 „Clinical Laboratory Assessments“.

10.3.1 Screening Visit

Written informed consent must be obtained from each subject before any study related procedures are performed. To initiate screening procedures, at least 72 hours must have elapsed since the last VWF administration for on-demand subjects and the subject must not be actively bleeding at the time of screening. For switch subjects, the usual interval between their pdVWF prophy infusions must have elapsed since the last VWF administration and the subject must not be actively bleeding at the time of screening. Multimer analysis and VWD gene mutation analysis should be performed at screening if not available in the subject's medical history.

The screening visit will be delayed if the subjects presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like symptoms, inflammatory diseases) until the event has resolved. All screening procedures and confirmation of eligibility shall take place within 42 days prior to the first infusion of IP. If the IP is not infused within 42 days, all screening assessments except blood group, human leukocyte antigen (HLA), genetics, multimeric pattern and [redacted], must be repeated to reconfirm eligibility. Refer to Supplement 20.2 and Supplement 20.3. Upon completion of screening procedures, subject eligibility will be confirmed by the sponsor on a subject eligibility form before additional study procedures are undertaken. The subject will maintain a diary that will include infusion logs (see Section 10.5). The allocation of IP will be initiated after the subject has qualified for home treatment (see Section 8.6.4.3.2).

In the event of a subject experiencing a bleeding episode that requires treatment between the screening visit and the subsequent visit (i.e. initial PK assessment visit for on-demand subjects or prophylaxis initiation visit for switch subjects), the subject will be treated with rVWF (vonicog alfa). If rVWF (vonicog alfa) is not available for any reason, e.g., subject not yet trained on IP administration, study site visit for IP administration not feasible, etc., the subject may use his/her standard of care, such as commercial pdVWF/FVIII products, and the reason for the use of non-IP products should be clearly documented.

10.3.2 Baseline Visit – Initial PK Assessment (On-demand Subjects Only)

After screening and confirmation of eligibility on-demand subjects will undergo an initial PK assessment. Subjects will receive a dose of 50 ± 5 IU/kg rVWF:RCo to determine VWF and FVIII levels. 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). See Section 20.2 and Section 20.3. IP infusion vials from the same lot number should be used for all PK-assessments per subject. Samples for measurement of FVIII and VWF activity taken through to 6 hours post-infusion will be obtained from an extremity different from that used for the infusion of IP. Where needed, the phlebotomy site will be kept patent via an infusion of normal saline. In this event, at least 5 mL of blood will be collected and discarded before collection of the next test sample into a fresh syringe.

If the subject has a central venous catheter, the central line should be used to administer the infusion and a peripheral venipuncture should be used to collect the blood samples.

In the event that a blood sample must be drawn through the central line used for administration of IP, the line must first be flushed with at least 10 mL normal saline or other suitable catheter flush solution that does not contain anticoagulant. At least 5 mL of whole blood must be collected and discarded prior to obtaining the sample.

If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.6.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment.

For pdVWF switch subjects, PK profile will not be assessed until reaching steady state after initiation of prophylaxis (see Section 10.3.4).

10.3.3 Prophylaxis Initiation Visit

The prophylaxis initiation visit will occur after the blood sample for the 96 hour PK assessment is drawn for on-demand subjects or within 42 days after screening and confirmation of eligibility for pdVWF switch subjects. The subject will receive the first rVWF (vonicog alfa) prophylactic dose of rVWF: RCo. Details on dose are provided in Section 8.6.4.3.

Procedures and assessments at this visit include (but are not limited to): AEs, bleeding episodes, medications taken, and non-drug therapies. Within 2 hours prior the IP infusion, a physical examination will be performed. Vital signs will be assessed within 30 minutes prior to IP rVWF (vonicog alfa) infusion and 30 minutes ± 15 minutes after IP infusion. Further details are provided in Supplement 20.2 and Supplement 20.3.

10.3.4 Initial Steady State PK-Assessment (pdVWF switch subjects only)

For pdVWF switch subjects, a full PK profile will be assessed at steady state conditions on two occasions. The initial PK assessment will be performed shortly after reaching steady state after starting prophylaxis dosing, which is suggested after 11 days post the 1st, around prophylaxis dose #5-6. The 2nd PK assessment at steady state will be performed at the end of the study.

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). In case the dosing schedule does not permit the 96 hr sampling, this sampling time point can be omitted (See Section 11.6). IP infusion vials from the same lot number should be used for all PK-assessments per subject.

Samples for measurement of FVIII and VWF activity taken through to 6 hours post-infusion will be obtained from an extremity different from that used for the infusion of IP. Where needed, the phlebotomy site will be kept patent via an infusion of normal saline. In this event, at least 5 mL of blood will be collected and discarded before collection of the next test sample into a fresh syringe.

If the subject has a central venous catheter, the central line should be used to administer the infusion and a peripheral venipuncture should be used to collect the blood samples. In the event that a blood sample must be drawn through the central line used for administration of IP, the line must first be flushed with at least 10 mL normal saline or other suitable catheter flush solution that does not contain anticoagulant. At least 5 mL of whole blood must be collected and discarded prior to obtaining the sample.

If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.6.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment. In case of surgery or bleeding, the PK assessment should be performed after 11 days after 1st prophylactic dose after re-start of prophylactic regimen. See section 11.6 for more details.

10.3.5 Treatment of Bleeding Episodes

Treatment of bleeding episodes is described in detail in Section 8.6.4.4 and treatment of perioperative bleeding is described in detail in Section 8.6.4.5.

10.3.6 Perioperative Visits (only applicable if surgery is needed)

The perioperative visits from priming dose through postoperative day 14 will be required to check daily intra- and postoperative weight-adjusted dose of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa). Details on the procedures and assessments performed at each visit can be found in supplement tables in Section 20.2.1 and Section 20.3.1.

10.3.7 Follow-Up Visits

Visits will be performed after the prophylaxis initiation visit at 1 month ± 1 week, 2 months ± 1 week, and 3 months ± 2 weeks and thereafter every three months ± 2 weeks. Additional visits may occur if clinically indicated (see Section 10.3.8).

When possible, site visits should be scheduled on days when the subject is expected to infuse rVWF (vonicog alfa). Within 2 hours prior to the rVWF (vonicog alfa) IP infusion, a physical examination will be performed. Vital signs will be assessed within 30 minutes prior to IP infusion and 30 minutes ± 15 minutes after IP infusion. Incremental recovery (IR) will be determined at each follow-up visit based on VWF:RCo activity assessed prior to and after IP infusion.

The blood sample for IR analysis will be drawn within 30 minutes prior to IP infusion and 30 minutes ± 5 minutes after IP infusion. rVWF (vonicog alfa) will be infused at the regular prophylactic dose. For each subject's recovery analysis IP infusion, vials from the same lot number should be used.

Testing for VWF:RCo VWF:CB, rVWF:Ag, and FVIII:C level will be performed using the blood sample obtained before and after IP infusion.

The blood sample prior to IP infusion will also be used for the assessment of neutralizing and binding antibodies, clinical chemistry and hematology. For on-demand subjects, a washout period of at least 72 hours after the last infusion applies before the blood draw for the immunogenicity assays. For switch subjects, the wash out period may be reduced to the time interval between their pdVWF prophy infusions Bleeding episodes and the hemostatic efficacy will be evaluated based on the review of the patient diary. See Section 20.2 and Section 20.3. The evaluation of IP consumption and treatment compliance will be performed based on subject's diary entries. If a subject is not compliant with the prophylactic treatment regimen and does not adhere to the required frequency of administration of IP infusions (>30% of infusions were missed within a visit interval [3 months]) the subject will be withdrawn from the study.

At the 6 months ± 2 week visit an ECG will be performed and [redacted] data will be collected.

For the hemostatic efficacy assessment the following information will be recorded by the subject in the patient diary: bleeding location, type, severity, onset and resolution date and time, infusion date and time, clinical efficacy according to the rating scale. If at any time during the study a subject's bleeding episode does not adequately respond to rVWF (vonicog alfa) therapy, he/she will be evaluated for the presence of neutralizing and total binding antibodies. Refer to Section 12.9.3.2.

Further guidance on completing the subject's diary will be provided to the subjects during training for home treatment (see Section 8.6.4.3.2).

10.3.8 Unscheduled Visits

For any unscheduled visit (except for collection of IP) a clinical assessment will be performed as per the scheduled follow-up visits with the exception of [redacted], ECG, and IR determination (refer to Supplement 20.2 and Supplement 20.3).

Subjects who have more than one bleeding episode in 3 months, or an increased frequency of bleeding, should go to the study site for an unscheduled visit.

Follow-up visits after the subject has experienced a bleed may be requested by the investigator. Additional assessments may be required which are at the discretion of the investigator.

10.3.9 End of Study PK Assessment and Study Termination Visit

At the 12* month ± 2 week visit, a full PK analysis at steady state will be performed for both cohorts: on-demand and switch subjects. 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) unless dosing schedule does not permit, in which case the 96 hr sampling can be omitted. If a subject experiences a bleeding episode during the PK assessment no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 8.6.4.4 has to be followed for the treatment of the bleeding episode. The subject once recovered is eligible to repeat the PK assessment and the PK assessment should be performed after 11 days after 1st prophylactic dose after re-start of prophylactic regimen. See section 11.6 for more details.

Refer to Supplement 20.2 and Supplement 20.3 for the other assessments to be performed at the PK assessment and study completion visits.

For on-demand subjects, a washout period of at least 72 hours is required between the PK infusion and the study termination visit (at the time of the 96 hour postinfusion PK assessment). For switch subjects, the wash out period may be reduced to the time interval between their rVWF (vonicog alfa) prophy infusions. Refer to Supplement 20.2 and Supplement 20.3 for the list of assessments to be performed at the termination visit.

Subjects will be offered the option to continue to receive rVWF (vonicog alfa) in a long-term continuation study*.

* Study treatment period is extended by 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. For subjects whose completion date is extended beyond the 12-month visit due to delay in continuation study start-up, the 12-month ± 2 weeks visit will be considered as a follow-up visit, and EOS visit will be performed once the subject can rollover into the continuation study, from 12 month ± 2 weeks to 15 month ± 2 weeks post prophylaxis initiation visit, as applicable. Both the 12-month ± 2 weeks visit rescheduled as a follow-up visit, and the rescheduled EOS visit will be recorded in the CRF.

10.4 Medications and Non-Drug Therapies

The following medications and non-drug therapies are **not** permitted within 30 days before study entry and during the course of the study:

Medications:

- 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) and an extended treatment period >3 months.
- Another investigational and/or interventional study drug (except rVWF and FVIII administered under the surgery protocol).

A subject who has taken any of these medications or received any of these non-drug therapies during the study will be withdrawn from the study.

The following medications are permitted during the course of the study:

- Antifibrinolytics (e.g., tranexamic acid, ε-amino caproic acid) or topical hemostats as needed, according to each institution's standard of care. These may be used, in accordance with local standard clinical practice, as the initial or only treatment for minor and moderate bleeding events. However, if the bleeding has not stopped within 24 hour following administration of this non-VWF treatment, infusion(s) with rVWF (vonicog alfa) should be started per protocol
- Emergent use of a VWF concentrate other than rVWF (vonicog alfa) may be permissible under certain circumstances (see Section 8.6.4.4.1)

Details of all adjunctive hemostatic medication used, including dose and reason for use, must be recorded in the eCRF.

10.5 Subject Diary

An electronic subject diary will be provided to each subject at the screening visit to record the following information:

1. IP infusions to include date, start and stop times of the infusion, number of vials utilized, and infusion volume for prophylactic treatment or treatment of spontaneous and traumatic bleeding episodes
2. Details of bleeding episodes (site, type, severity and date/time of bleeding) and response to treatment as described in Section 8.6.4.4
3. Subjective hemostatic efficacy assessments
4. Untoward events/unwanted experiences
5. Concomitant medications (including immunizations) and non-drug therapies
6. Patient Reported Outcomes (PROs)

Subjects and/or their legally authorized representatives will be trained on use of the diary. The diary will be provided in electronic format and remain with the subject for the duration of the study. The investigator will review the diary for completeness and request missing information periodically and in a timely manner. The investigator will record/capture any unwanted experience reported by the subject which may qualify as an AE on the AE eCRF.

Infusions performed at the study site will first be recorded in the site's source documents and not in the patient diary.

Subject entries in the diary will serve as source records. During study participation the investigator has access to the database holding the subject diary data. After study closure, the investigator will receive the diary records for their subjects, including audit trail records, in PDF format. The data will be transmitted to the CRF by a validated transfer.

Paper diary may be utilized in rare case where electronic diary use is not possible.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have completed all study procedures according with the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, AE (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, e.g., technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the study termination visit. If the termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the termination visit.
If a subject terminates participation in the study and does not return for termination visit, his/her last recorded assessments shall remain with the last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.2 Schedule of Study Procedures and Assessments and Supplement 20.3 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

10.7 Procedures for Monitoring Subject Compliance

Subject compliance with the procedures of this study (treatment regimens and study visits) will be monitored by the investigator or/a licensed healthcare professional at the study site.

During the regular scheduled follow-up visits a direct review of the subject's source data (e-diaries) will be performed at the sites and evaluated against the protocol requirements. In addition drug accountability will be evaluated at each follow-up study visit and the study termination visit by comparing the infusions recorded in the subject diary with empty vials returned by each subject to the study site, and the study site's dispensing record. Protocol deviations will be noted in the final report.

11. ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

11.1 Assessment of Spontaneous Bleeding Episodes/Annualized Bleed Rate

The annualized bleed rate (ABR) will be assessed based upon each individual spontaneous bleed, requiring coagulation factor replacement therapy, i.e., rVWF (vonicog alfa) treatment. The following details on bleeding episodes will be recorded by the subject in the electronic diary (for home treatment), the subject's healthcare provider in the site's source documents (for treatments away from the primary investigative site), or by authorized, qualified personnel at the participating site in the subject's medical records (for hospital-based treatment):

- Location of bleed; i.e., joint, menorrhagia, epistaxis, gastrointestinal, soft tissue, muscle, body cavity, intracranial, etc.
- Type of bleed; i.e., spontaneous, traumatic, unknown
- Severity of bleed; i.e., minor, moderate, and major (see Table 3)
- Date and time of onset of bleed
- Date and time of each infusion of rVWF (vonicog alfa) or rVWF (vonicog alfa)-ADVATE (rFVIII, octocog alfa) used to treat a bleeding episode
- Date and time of resolution of the bleeding episode

Study site personnel are qualified after they have undergone training during the qualification of the site.

All types of bleeds, including traumatic bleeds, will be recorded. Bleeding episodes should be organized by where they occur in addition to whether they occurred spontaneously or due to a traumatic event.

Bleeds occurring at the same anatomical location (e.g., right knee) with the same etiology (i.e., spontaneous versus injury) within 24 hours after onset of the first bleed will be considered a single bleed. Bleeding occurring at multiple locations related to the same injury (e.g., knee and ankle bleeds following a fall) will be counted as a single bleeding episode.

All efforts should be made to use rVWF (vonicog alfa) for treatment of bleeding episodes. If needed, the use of a VWF concentrate other than IP for the treatment of bleeding episodes will not disqualify the subject from further participation in the study.

11.2 Evaluation of ABR Before rVWF Prophylaxis and ABR Under rVWF Prophylactic Treatment

At screening, the subject's medical history will be recorded, including the number and location of all spontaneous and traumatic bleeding episodes within the past 12 months (up to 24 months if available). The maximum interval of bleed-free periods as well as trauma induced bleeding episodes will also be recorded (prospectively and retrospectively).

11.3 Number of Infusions and Total Weight Adjusted Consumption of rVWF and ADVATE and historical prophylaxis dosing and factor consumption during pdVWF prophylaxis treatment prior to enrollment

The number of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) (in case of bleeding episode treatment) infusions will be logged in the subject diary. Based on these entries the weight adjusted consumption will be calculated.

At the screening, historical pdVWF dosage and dosing frequency during 12 and up to 24 months of pdVWF prophylactic treatment prior to enrollment will be recorded for the pdVWF switch subjects in order to calculate the consumption of pdVWF.

11.4 Assessment of Efficacy for Treatment of Bleeding Episode

Investigators will be asked to assess and record hemostatic efficacy after resolution of each bleeding episode using the 4-scale rating system outlined in Table 4.

Table 4
Efficacy Rating Scale

Rating	Efficacy Rating Criterion	
	Minor and Moderate Bleeding Events	**Major Bleeding Events**
Excellent (=1)	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF containing coagulation factor containing product required	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF containing coagulation factor containing product required
Good (=2)	1-2 infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required	< 1.5 x infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required
Moderate (=3)	3 or more infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required	≥ 1.5 x infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation factor containing product required
None (=4)	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF containing coagulation factor containing product required	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF containing coagulation factor containing product required

11.5 Assessment of Efficacy for Treatment for Surgical Bleeding

For those undergoing surgery, the operating surgeon will be asked to assess and record actual versus predicated blood loss and intraoperative hemostatic efficacy immediately after surgery.

The investigator will be asked to assess and record an overall assessment of hemostatic efficacy 24 hours after the last perioperative rVWF (vonicog alfa) infusion or at day 14 post-operation, whichever occurs first, using the 4-scale rating system described in Table 5.

Table 5
Assessment of Hemostatic Efficacy

Rating	Overall Assessment of Hemostatic Efficacy 24 Hours After the Last Perioperative rVWF Infusion
Excellent (1)	Intra- and post-operative hemostasis achieved with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) was as good or better than that expected for the type of surgical procedure performed in a hemostatically normal subject
Good (2)	Intra- and post-operative hemostasis achieved with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) was probably as good as that expected for the type of surgical procedure performed in a hemostatically normal subject
Moderate (3)	Intra- and post-operative hemostasis with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) was clearly less than optimal for the type of procedure performed but was maintained without the need to change the rVWF (vonicog alfa) concentrate
None (4)	Subject experienced uncontrolled bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of rVWF (vonicog alfa) concentrate

11.6 rVWF Pharmacokinetics and Pharmacodynamics

PK will be assessed twice for all subjects.

For on-demand subjects, an initial PK assessment using a dose of 50 IU ± 5 IU/kg rVWF:RCo will be performed at the baseline visit, and 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 week 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 assay. 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 assessment using the subject's individualized dose will be performed shortly after reaching steady state, which is estimated to be reached for the majority of subjects after approximately 11 days from the 1st prophylactic dose. To fit any logistical requirements, samples for PK analysis can be taken after prophylaxis dose #5-6, and whenever possible, sample collections should be during the longer partial interval of the alternating irregular dosing intervals. For example, if a subject follows a dosing regimen as follows:

Date	Weekday	Dose number	Interval	Time from 1st 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 profile will be assessed at the end of the study, i.e. 12* month ± 2 week visit with a PK 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 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). If the dosing interval for a certain switch subject wouldn't allow for the full 11 post-infusion timepoints sample collection, 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 for an individual switch subject.

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

* Study treatment period is extended by 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.

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

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, whether or not considered causally related to the IP.

12.1.1.1 Serious Adverse Event

An SAE is defined as an untoward medical occurrence that, at any dose, meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are (including but not limited to):
    - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
    - Reviewed and confirmed seroconversion for HIV, hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)

- Development of clinically significant neutralizing VWF antibodies
- Development of neutralizing antibodies to FVIII (titer ≥0.4 BU [by Nijmegen- modified Bethesda assay] or ≥0.6 BU [by Bethesda assay])
- Thromboembolic events (e.g., myocardial infarction, stroke, transient ischemic attack [TIA], deep vein thrombosis [DVT] or pulmonary embolism)
- Hypersensitivity reactions (e.g., anaphylaxis [for definition, refer to Section 12.6.2] and other immediate and delayed hypersensitivity reactions which may manifest with urticarial rash, pruritus, flushing, angioedema of the face, extremities, or laryngeal tissues [leading to throat tightness with stridor], wheezing, gastrointestinal symptoms, and/or hypotension)

Uncomplicated pregnancies, following maternal or paternal exposure to IP are not considered an AE/SAE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE and should be reported per SAE reporting guidelines provided in Section 12.1.2.3 (Safety Reporting).

12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any suspected adverse reaction to study treatment that is both serious and unexpected is considered a SUSAR.

The event(s) must meet all of the following:

- Suspected adverse reaction (which implies that there is reasonable evidence indicating a causal relationship between the event and the study treatment),
- Unexpected (per Reference Safety Information (RSI)/IB), and
- Serious

Once determined to meet the criteria for a SUSAR, the sponsor will ensure expedited SUSAR reporting is completed in line with the regulatory requirements in participating countries as outlined in the Safety Management Plan.

12.1.1.3 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet any of the seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) listed in section 12.1.1.1.

12.1.1.4 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (e.g., IB, PI [prescribing information]). "Unexpected" also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.1.1.5 Preexisting Disease

Preexisting diseases that are present before entry in to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described as "worsening" of the pre-existing condition on the AE CRF.

12.1.2 Assessment of Adverse Events

For the purposes of this study, the following will not be considered as AEs and will not be included in the analysis of AEs.

- Bleeding episodes are part of the underlying disease and therefore are not AEs; they will be evaluated in the context of efficacy.
  - For non-serious bleeding episodes caused by an injury, the injury would not be reported as an AE, unless it resulted in a medical finding other than a bleeding episode (e.g., abrasion of skin). Therefore, any VWD-related bleeding event (e.g., epistaxis, gastrointestinal bleeding, musculo-skeletal bleeding, menorrhagia) that is non-serious will not be reported as an AE. However, the investigator may decide that the event is an AE if the event also would have occurred in a healthy individual under the same circumstances.
  - For serious bleeding episodes (bleeding SAEs): Bleeding events that meet seriousness criteria (death, life-threatening, hospitalizing/prolongation of hospitalization, disability, congenital anomaly, or medically significant and if not urgently treated would result in one of the above) should be captured on the SAE eCRF and reported as an SAE to the Sponsor or designee (e.g., CRO) on an SAE Report form as described in Section 12.1.2.3 (Safety Reporting).
- Seroconversion after documented HAV/HBV vaccination prior to or during the study period.

Each AE from the first IP exposure to the study completion date will be described on the AE CRF using the term representing medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial verbatim expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2

For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable, action taken with regards to the study treatment (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution or until the subject's condition returns to the level at the baseline for pre-existing conditions.

If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the protocol-specified dosage (including underdosing /overdosing [<20 IU/kg rVWF:RCo or >100 rVWF:RCo], abuse, and withdrawal, treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after administration of IP will be reported on a Pregnancy Form and followed-up at 1 year post-delivery, if feasible.

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the SAE Form within 24 hours after awareness: no additional reporting on CRFs is necessary.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, e.g., assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs

- Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP, is not biologically plausible per mechanism of action of the IP, or has a much more likely alternative etiology).

- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of IP
  - An alternative etiology is equally or less likely compared to the potential relationship to the IP
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
    - Reappearance of a similar reaction upon re-administration (positive re-challenge)
    - Positive results in a drug sensitivity test (skin test, etc.)
    - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
  - Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within 5 days after IP infusion, the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

12.1.2.3 Safety Reporting

AEs and SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Section 20.2) and Section 12.1.2.

Adverse Events and SAEs are to be recorded on the AE page of the eCRF. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the IP, must be reported immediately (within 24 hours of the study center's first knowledge of the event). All SAEs must be reported in English via the Electronic Data Capture (EDC) system by completing the relevant eCRF page(s) and also by SAE Report Form via fax/email to Sponsor's Global Drug Safety (Baxalta GDS) department within 24 hours of becoming aware of the event for SAEs (for contacts, instructions, and additional details, refer to the SAER form).

Within 24 hours of site awareness of a SAE (or Pregnancy) study sites will complete and send all SAE (or Pregnancy) reports to a dedicated:

Baxalta Global Drug Safety fax number: [redacted]

OR

email: [redacted]

The responsible Site Monitor will review the SAE (or Pregnancy) Reports for completeness, will reconcile the reports against the EDC database, and will follow-up with sites to obtain missing information and/or information requiring clarification. Any SAE associated with a pregnancy must be reported on the SAER Form.

For Follow-up Reports, the site shall use a new SAER form (marked as Follow-up) and the new information should be entered together with a brief narrative identifying the updated data.

An SAER should include the following minimum information:

1. Protocol Number (on all pages)
2. Subject identification number (on all pages) and demographics (gender, age at onset of event and/or date of birth)
3. Investigational product and treatment regimen (including date of the first dose of IP, date of the last dose of IP prior to the onset of the SAE)
4. Medical Term for Event (Diagnosis preferably)
5. Description of the SAE, including:
    - Date of onset
    - Causal relationship assessment by the Investigator
6. Seriousness criteria (e.g., death, life-threatening, hospitalization, medically significant, or other criterion)
7. Name, address, fax number, email, and telephone number of the reporter/Investigator

Post-trial SAE Reporting: In compliance to EudraLex Volume 10 (Clinical trials guidelines, Chapter II: Safety Reporting from the European Commission), which references an EMA guidance (ICH Topic E 2 A - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting), clinical sites/the investigator should report to the Sponsor SAEs after a subject´s study completion. Study sites will be provided a Post-Trial SAER form to complete and report these post-study SAEs to the Sponsor within the 24 hours of their awareness. Site Monitor will instruct the site that any such Post-Trial SAEs should be reported on the study-specific Post-Trial SAER form if/when the site becomes aware of it. Such information will not be actively monitored by the sponsor after completion of the study.

These events shall be reported to Baxalta GDS who will process them in the same way as SAEs occurring during the study. Post-Trial SAEs do not need to be captured in the study EDC database if it is already locked. Irrespective if captured in the EDC database or not, such Post-Trial SAEs will become part of the GDS database. The monitor should remind the clinical site about the post-trial SAE reporting requirements during interim monitoring visits, upon each subject's study completion as well as during the close-out visit.

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of the clinical trial
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor.
In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committees (ECs) and relevant competent authority(s) are notified of the urgent measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (i.e., from the time of signed informed consent up to but not including the first IP exposure) will be described on the SAER. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE.** NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g. reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (e.g., potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) 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. The subject's medical history will also include documented history of on-demand or pdVWF prophylaxis treatment for at least the past 12 months and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 months (up to 24 months if available).

All medications taken and non-drug therapies received in the 2 weeks prior to study entry and all concomitant medications and non-drug therapies during study will be recorded on the CRFs.

Data on medical history, drug and non-drug therapy history of those subjects who transition from surgery rVWF (vonicog alfa) study will be used from the eCRF of the main studies, will be updated, if applicable, and transcribed into the respective eCRF of the prophy study.

12.6 Physical Examinations

At screening and subsequent study visits (as described in Section 10.3), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 12.1.1.5), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.6.1 Thromboembolic Events

There is a risk of occurrence of thrombotic events, particularly in patients with known clinical or laboratory risk factors for thrombosis including low ADAMTS13 levels. Therefore, patients at risk must be monitored for early signs of thrombosis during the study and prophylaxis measures against thromboembolism should be instituted according to current recommendations and standard of care. Additional diagnostic procedures are required according to each institution's standard of care which may consist of, but are not limited to the following:

- For DVT: Magnetic Resonance Imaging (MRI), compression ultrasound or impedance plethysmography.
- For pulmonary embolism: ECG, chest radiography, perfusion/scintiscan or MRI.
- For myocardial infarction: ECG, cardiac enzymes, echocardiography
- For stroke: diffusion-weighted magnetic resonance imaging or computed tomography, ABCD scoring, carotid imaging

Results of diagnostic procedures may be forwarded to the sponsor to be reviewed by an independent external expert panel, such as the DMC, if applicable.

12.6.2 Anaphylaxis

The diagnosis of anaphylaxis is highly likely when any of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g, generalized urticaria, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
    b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a. Involvement of the skin or mucosal tissue (e.g., generalized urticaria, pruritus or flushing, swollen lips-tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c. Reduced BP or associated symptoms (hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to a known allergen for that patient (minutes to several hours):
    a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
    b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP

If a subject develops anaphylaxis in the course of the clinical study, this needs to be reported as SAE (Section 12.1.1.1). Additional blood will be drawn for Anti-VWF IgE antibody testing (Section 12.9.13).

12.7 Vital Signs

Vital signs will be assessed pre- and post-infusion at each visit, if not stated otherwise:

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

Vital signs (pulse rate, respiratory rate, and blood pressure) should be recorded within 30 min before and after IP administration. The assessment of vital signs per planned study visit is outlined in Supplement 20.2.

Vital sign values are to be recorded on the physical examination eCRF. For each vital sign value, the investigator will determine whether the value is considered an AE (see definition in Section 12.1). If assessed as an AE, the medical diagnosis (preferably), symptom, or sign, will be recorded on the AE eCRF. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE, should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.8 Electrocardiogram

A standard 12-lead ECG at rest will be performed at screening, at the 6 month follow-up visit and at the study termination visit and evaluated for medical significance by the investigator.

12.9 Clinical Laboratory Parameters

Refer to the Laboratory Manual for information on collection and processing of samples.

In general all laboratory tests will be performed at central laboratories, except the pregnancy and blood group test which will be performed at the local laboratory. In addition, relevant critical safety laboratory tests for complete blood count (CBC), serum chemistry and/or coagulation parameters such as VWF and FVIII activity may also be performed in the local laboratory to ensure that results will be available immediately to the investigator. In principle, results from the central laboratory will be used for data analysis purposes. The assays performed in the central laboratories are specified in the Laboratory Manual. The investigator will supply the sponsor with a list of the normal ranges and units of measurement for the laboratory variables to be determined at the site. Laboratory values such as antibodies to other proteins are not required immediately and will be assessed later during the course of the study.

Any abnormal laboratory value that is considered clinically significant by the investigator based on a local laboratory test result (reference range and the units to be provided) should be confirmed by a central laboratory test result for which the sample is drawn/collected within 24 hours of the abnormal finding by the local laboratory.

12.9.1 rVWF Pharmacokinetics and Pharmacodynamics

Details on pharmacokinetic and pharmacodynamics assessments are provided in Section 11.6.

12.9.2 Hematology and Clinical Chemistry

The hematology panel will consist of CBC [hemoglobin, hematocrit, erythrocytes (ie, red blood cell count [RBC]; mean corpuscular volume [MCV], mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration [MCHC]), and leukocytes (i.e., white blood cell count [WBC])] with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.

The clinical chemistry panel will consist of sodium (Na), potassium (K), chloride (Cl), ALT, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase (AP), blood urea nitrogen (BUN), CR, and glucose (Glu).

Blood will be obtained for assessment of hematology and clinical chemistry parameters at screening, during PK-assessment prior to rVWF (vonicog alfa) IP infusion, after 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours post rVWF (vonicog alfa) IP infusion, at all follow-up visits as per schedule (refer to Supplement 20.3 Clinical Laboratory

Assessments), i.e., 4 weeks ± 1 week, 8 weeks ± 1 week and every 3 months ± 2 weeks, and at study completion. Hematology and clinical chemistry assessments will be performed on Ethylenediaminetetraacetic acid (EDTA)-anticoagulated whole blood and serum, respectively, at the central laboratory.

12.9.3 Immunology

12.9.3.1 Antibodies to VWF and FVIII

All subjects will be tested for binding and neutralizing antibodies to VWF and FVIII at screening, at initial PK assessment, at each of the scheduled follow-up visits and at the study completion visit. Testing will be done prior to IP infusion and with at least a 72 hour wash out period since the last IP infusion. If there is any suspicion of inhibitor development (e.g. excessive bleeding) binding and neutralizing antibodies to VWF and FVIII may be tested at the discretion of the investigator.

12.9.3.2 Neutralizing and Total Binding Anti-VWF Antibodies

The assays to establish the presence of neutralizing and total binding anti-VWF antibodies have been established in the absence of international standards and with only limited numbers of positive controls. Therefore, caution is advised in interpreting positive results. In particular, any clinical association, changes in the natural history of the disease, effect of therapy, etc. needs to be taken into account for final judgment. The sponsor's Medical Director should be consulted for additional advice. As part of the AE follow-up, any sample testing positive needs to be confirmed after 2-4 weeks for central laboratory testing. Only confirmed neutralizing anti -VWF antibodies are considered inhibitors (see Section 12.9.3.4). These subjects need to be closely monitored and therapy adjusted accordingly.

12.9.3.3 Binding antibodies to VWF

The presence of total binding anti-VWF antibodies will be determined by an enzyme-linked immunosorbent assay (ELISA) employing polyclonal anti-human Immunoglobulin (Ig) antibodies (IgG, IgM and IgA). For this assay (ELISA), recombinant human VWF will be coated onto a microtiter plate, then incubated with dilutions of the positive control, the negative control or test sample. Antibodies against human VWF that are present in the samples bind to the coated antigen and will be detected with a horseradish peroxidase (HRP)-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a human monoclonal antibody specific for human VWF spiked into the negative control. The negative control for this assay is pooled normal human plasma.

Plasma samples are analyzed for binding antibodies against the specific antigen in two steps. First, the sample is screened for antibodies and the titer of binding antibodies is determined. Second, the specificity of positive antibody results is confirmed.[16]
In brief, all samples are serially diluted (initial dilution 1:20 and further diluted 1:2).

The titer endpoint, defined as the highest dilution that still gives a positive signal above cut off level, is determined in two independent duplicates. The cut off level is established based on background signal level of healthy plasma donors (n=160) and set to include 5% false positives to be as sensitive as possible (95% percentile). The ELISA assay is validated allowing an assay variability of ± 1 titer step. Therefore, differences ≤ 2 titers steps may be due to variability of the ELISA assay. Specificity has to be confirmed in a competition assay when a sample has a titer of 1:80 or higher in the screening assay. Based on the validation criteria samples tested in the screening assay at 1:20 or 1:40 cannot be confirmed in the competition assay. A positive screening value is confirmed if the difference between the titers determined for the subject sample (re-screen) and for the subject sample with pre-incubation (confirmation sample) is > 2 titer steps. Antibody titers of subject samples will only be reported as positive, if the results of the screening and confirmatory analysis fulfill these acceptance criteria. The titer to be reported is always the one determined in the original screening procedure (independent of the result of the re-screening in the confirmation procedure).

A more detailed test procedure will be supplied upon request or pro-actively if a sample tests positive. A treatment related increase of the binding anti-VWF antibodies is expected, if the titer increases by more than 2 titration steps. These subjects need to be closely monitored and therapy adjusted accordingly.

12.9.3.4 Neutralizing Antibodies to VWF

Three functional VWF assays, VWF:CB, VWF:RCo and VWF:FVIIIB assays, will be used to test for the presence of neutralizing anti-VWF antibodies. Neutralizing antibodies to VWF:RCo, VWF:CB and VWF:FVIIIB activities will be measured by assays based on the Bethesda assay established for quantitative analysis of FVIII inhibitors (Nijmegen modification of the Bethesda assay).[17] The amount of inhibitor is expressed as BU per mL. One BU is thereby defined as the amount of inhibitor that decreases the measured activity in the assays to 50% of that of the negative control samples. The assays were validated using human plasma samples from two type 3 VWD patients with low (1-2 BU/mL) and high (~10 BU/mL) titer inhibitors and plasma samples from non-human primates immunized with human rVWF (vonicog alfa) (>100 BU/mL).

If a subject has a measurable baseline level of VWF activity in the respective assay, it is taken into account in the calculation of the residual activity. However, if baseline levels are too high (>15% VWF:RCo), inhibitors may not be reliably detected.

To exclude false positive results, the detection limit for anti-VWF inhibitors was set to 1 BU/ml for all 3 assays. The rationale for this cut-off value is the relatively high CI of the underlying assays, making determinations at the end of the evaluation range of the Bethesda reference curve uncertain.[18] A more detailed test procedure may be requested to further characterize the anti-VWF inhibitors, if detected.

Only confirmed positive anti-VWF inhibitor test result will be reported and will be considered as a medically significant SAE.

12.9.3.5 Binding Antibodies to FVIII

Binding antibodies against FVIII will be analyzed using a proprietary enzyme immunoassay. The testing strategy will be as described for binding anti-VWF antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.3.6 Neutralizing Antibodies (Inhibitors) to FVIII

Neutralizing antibodies (inhibitors) to FVIII will be assessed by the Nijmegen modification of the Bethesda assay in a central laboratory. To verify a FVIII inhibitor, additional testing (such as tests for Lupus anticoagulants) may be initiated. Positive FVIII inhibitor tests will be defined as $\geq$ 0.4 BU by the Nijmegen-modified Bethesda assay that is confirmed by a second test performed on an independent sample obtained 2-4 weeks following the first test. Only confirmed positive FVIII inhibitor test result will be reported.

12.9.4 Antibodies to Other Proteins

Plasma will be assayed for the presence of antibodies against CHO protein (total Ig), murine IgG and human Furin (total Ig) using proprietary enzyme immunoassays. The testing strategy will be as described for binding anti- VWF antibodies. Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.4.1 Anti-CHO Protein

Total Ig antibodies (IgG, IgA, IgM) against CHO protein will be analyzed. For this assay (ELISA), CHO protein derived from cultures of untransfected cells and propagated under the identical cell culture conditions used for ADVATE (rFVIII, octocog alfa) production will be coated onto a microtiter plate, then incubated with dilutions of the positive control, negative control or test sample. Antibodies against CHO protein that are present in the samples bind to the coated antigen and will be detected with a HRP-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a polyclonal goat anti-CHO protein antibody spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.4.2 Anti-Murine IgG

A commercially available ELISA (Medac, Hamburg, Germany) will be used to detect and to quantify IgG antibodies originating from human plasma that are directed against mouse-IgG (HAMA: human anti- mouse antibodies). Microtiter plates coated with mouse IgG will be incubated with dilutions of the standard, the positive control, the negative control or the test sample. Antibodies against mouse IgG that are present in the samples bind to the coated antigen and form a bridge to a peroxidase coupled mouse IgG antibody that will be used for detection (bridging format of the ELISA assay). The positive control for this assay will be a polyclonal goat anti-murine IgG spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.4.3 Antibodies to Human Furin

Total Ig antibodies (IgG, IgA, IgM) against human Furin will be analyzed. For this assay (ELISA), recombinant human Furin will be coated onto a microtiter plate, then incubated with dilutions of the positive control, the negative control or test sample. Antibodies against human Furin that are present in the samples bind to the coated antigen and will be detected with a HRP-coupled goat anti-human antibody (secondary antibody). The positive control for this assay will be a human monoclonal antibody specific for human Furin spiked into the negative control. The negative control for this assay is pooled normal human plasma.

12.9.5 Viral Serology

The following viral seromarkers will be assessed at screening:

- HIV: anti-HIV 1, HIV 2
- HAV: anti-HAV (IgG and immunoglobulin M [IgM])
- HBV: Hepatitis B surface antigen (HbsAg), anti-Hepatitis B (HB) core, anti-HBs

- HCV: anti-HCV ELISA
- Parvovirus B19: anti-B19V (IgG and IgM)

Virus serology will be established during the screening period. The relevant confirmatory Polymerase Chain Reaction (PCR) testing may be performed from appropriate left-over samples as needed.

12.9.6 Urinalysis (Dipstick)

The urinalysis will include assessments for erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite and pH and will be performed at the central laboratory.

12.9.7 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. The pregnancy test may need to be repeated during the course of study in countries where mandated by national law.

12.9.8 VWD Mutational Analysis, Multimer Analysis and Human Leukocyte Antigen Genotyping

A cell pellet (buffy coat and erythrocytes) will be retained at the screening visit for VWD gene mutational analysis, VWF multimer analysis and HLA genotype determination if the information is not already available in the subject's medical history. Results from multimer analysis (see Section 12.9.10.1) may contribute to VWD gene mutational analysis. The genetic testing will be done, when the subject consents to the genetic testing.

12.9.9 Blood Group Analysis

The blood group needs to be determined during the screening period. If the information is not already available in the subject's medical history, it has to be determined at the local lab.

12.9.10 Additional Laboratory Testing in Case of Thromboembolic Events

rVWF (vonicog alfa) contains ULMW multimers because of a lack of exposure to endogenous VWF protease (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) during the manufacturing process. In vitro and in vivo cleavage of these ultralarge molecular fractions by ADAMTS13 and generation of characteristic satellite bands has been extensively demonstrated during nonclinical and clinical development. Nevertheless, the potential elevated risk of thrombosis and/or other thromboembolic complications due to the administration of ultra large molecular VWF multimers in subjects with normal levels of VWF cannot be completely excluded. Therefore VWF multimer analysis will not only be performed routinely at screening but in case of thromboembolic events, both VWF multimer analysis as well as ADAMTS13 activity will be determined to assess any relatedness of these occurrences with IP treatment.

12.9.10.1 VWF Multimer Analysis

The VWF multimer pattern will be assessed using low-resolution sodium dodecyl sulfate (SDS)–agarose gel electrophoresis. High-resolution SDS–agarose gel electrophoresis, with agarose concentrations >1.5%, will be used to determine the satellite band structure of VWF. These analyses will employ Western blot with luminescence video imaging.

12.9.10.2 ADAMTS13 Activity

VWF73 was identified as the 73 amino acid minimal region of the VWF A2 domain required for ADAMTS13 cleavage. The cleavage of this substrate will be detected by a commercially available ELISA-based Chromogenic assay (Technoclone Austria): Cleavage of immobilized VWF73 substrate is detected by a HRP-labeled antibody directed against the cleavage site of VWF73. The amount of bound antibody, which is the function of the ADAMTS13 cleavage is detected by a chromogenic substrate.

12.9.11 Soluble P-Selectin (sP-Selectin)

sP-selectin is a cell adhesion molecule (CAM) found in granules in endothelial cells (cells lining blood vessels) and activated platelets. Data for an association between the sP-selectin concentration, TTP and venous thromboembolism (VTE) are limited and the predictive value has not yet established. A commercial ELISA assay will be employed as an exploratory test. sP-selectin will be determined at the Screening visit and used as indicator for an increased thrombotic risk.

12.9.12 D-Dimer

D-dimer will be used as a marker for DVT and disseminated intravascular coagulation (DIC). While a negative result practically rules out thrombosis, a positive result can indicate thrombosis but does not rule out other potential etiologies, including a recent hemorrhage. Its main use, therefore, is to exclude thromboembolic disease where the probability is low. D-Dimer will be measured at the Screening visit and used as indicator for an increased thrombotic risk.

12.9.13 Additional Laboratory Testing in Case of Severe Hypersensitivity Reactions

If a subject develops a severe hypersensitivity reaction in the course of the clinical study, additional blood will be drawn for anti-VWF IgE antibody testing. The presence of anti-VWF IgE will be determined by using the ImmunoCAP®, a VWF-specific IgE blood test (Thermo Scientific). The basis of the ImmunoCAP® technology is a cellulose polymer as solid phase in a plastic capsule providing a large surface for protein binding. rVWF (vonicog alfa) as antigen is covalently coupled to the cellulose polymer.

Detection of specific anti-VWF IgE bound to the antigen will be accomplished by a secondary enzyme-labeled anti-human IgE antibody. Testing for binding anti-human VWF IgE antibodies will be done with 0.5 mL plasma. Antibody containing samples will be identified and quantified in a screening assay followed by a confirmatory assay to exclude false positive results.

12.9.14 Assessment of Laboratory Values

12.9.14.1 Assessment of Abnormal Laboratory Values

For VWF and FVIII laboratory assessments no evaluation of clinical significance is necessary.

Each other laboratory value (except results to determine genetics of the underlying VWD disease and blood group) has to be assessed by the investigator and the assessment will be recorded on the eCRF. The investigator will determine for each abnormal laboratory value whether the value is considered clinically significant or not and provide the reference range including the units. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 12.1) and record the sign, symptom, or medical diagnosis on the AE CRF, is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.5), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, i.e. because it is due to a preexisting disease, due to a lab error, due to variation or due to another issue that will be specified.

Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator. Any abnormal laboratory value that is considered clinically significant by the investigator based on a local laboratory test result (reference range and the units to be provided) should be confirmed by a central laboratory test result for which the sample is drawn/collected within 24 hours of the abnormal finding by the local laboratory.

Any seroconversion result for HIV, HAV, hepatitis B virus (HBV), HCV, HEV, or B19V shall be re-tested.

12.10 [redacted]

12.10.1 [redacted]

12.10.2 [redacted]

[redacted]

13. STATISTICS

13.1 Sample Size and Power Calculations

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 cohort (OD and switch). A total of at least 5 type 3 VWD subjects will be followed for 12 months. 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).[1]

13.2 Datasets and Analysis Cohorts

13.2.1 Safety Analysis Set

The Safety Analysis Set will be composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

13.2.2 Full Analysis Dataset

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

13.2.3 Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set will be composed of subjects who are at least 70% compliant regarding the number of scheduled prophylactic infusions (as measured by the ratio of actual number of infusions to planned number of infusions). Only subjects who met all study entry criteria and who had no major protocol violations that might impact primary efficacy assessments will be included in the PP analysis set.

13.2.4 PK Full Analysis Set

The Pharmacokinetic Full Analysis Set (PKFAS) will be composed of all subjects who received the PK infusion and who provided acceptable data for PK and PD analysis. Acceptable PK/PD data will be defined in the Statistical Analysis Plan.

13.2.5 PK Per Protocol Analysis Set

The Pharmacokinetic 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 affecting the PK period of the study as defined in the detailed Statistical Analysis Plan.

13.3 Handling of Missing, Unused, and Spurious Data

13.3.1 General

Statistical techniques will not be used to identify and exclude any observations as outliers from the analyses. If data are considered spurious, e.g. for lack of biological plausibility, it will be documented to include the reason for exclusion and the analyses from which the data were excluded.

13.3.2 Other

1. Regarding missing data in PK records:
    - Body weight: If a subject's weight is missing from the PK infusion record, the subject's last recorded weight will be used to calculate the weight-adjusted dose.
    - Concentration:
        - Baseline concentration levels reported as below the limit of quantification will be considered to be 0. Missing VWF baseline concentration levels (VWF: RCo, VWF: AG or VWF: CB) for Type 3 subjects will be set to 0.
    - Time:
        - If start time of infusion is missing (but stop time is available) and actual collection time is available, then stop time of infusion will be taken for further calculation (i.e. time difference between actual end date/time of infusion and date/time blood sample drawn).
        - If actual collection date/time is missing and planned collection date/time is missing, then this PK time point will be taken out from the PK analysis (i.e. no data entry for this time point).
        - For all other scenarios, the planned collection date/time will be taken for further calculation.
2. Regarding missing data in AE records:
    - Handling of unknown causality assessment:
        - If a subject experiences an AE with a missing causality assessment, the relationship of the AE will be counted as "related."

- Handling of unknown severity grades:
  - If a subject experiences more than one AE categorized under the same preferred term, 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.

13.4 Methods of Analysis

The study success criteria are the objectives as stated in Section 7. “Treatment success” was defined as the extent of control of bleeding episodes achieved during this study.

13.4.1 Primary Outcome Measure

The primary outcome measure is ABR for spontaneous (not related to trauma) bleeding episodes during prophylactic treatment with rVWF (vonicog alfa). No formal statistical hypothesis test is planned for the analysis. The primary efficacy analysis will be based on the FAS and will be summarized by the two cohorts: on-demand and switch subjects. As a supportive analysis, the same analysis will also be carried out on the PP analysis set.

The spontaneous ABR while treated with rVWF (vonicog alfa) for each cohort will be estimated using a negative binomial regression. The prior ABR will be based on historical data collected from each enrolled subject.

The two ABRs (prior to prophylaxis treatment and while on prophylaxis) for each cohort will be compared within each subject using a generalized linear mixed-effects model (GLMM) (with a logarithmic link function, the default for the negative binomial distribution), accounting for the fixed effect of the two treatments. The follow-up time (in years) will be specified as an offset. The ratio of ABR while in the study to historical ABR will be estimated and reported together with the 95% confidence interval for each of the two cohorts.

The difference in on-study ABR relative to historical ABR will be also summarized descriptively.

13.4.2 Secondary Outcome Measures

In general, data for secondary efficacy analysis will be summarized by the two cohorts: on-demand and switch subjects and when applicable overall. Mean, standard deviation, median, range, quartiles will be calculated for continuous endpoints. Proportions, will be calculated for categorical endpoints. Confidence intervals at the two-sided 95% level will be provided when appropriate.

13.4.2.1 Additional Efficacy of Prophylaxis Treatment with rVWF

The number and proportion of on-demand subjects with ABR percent reduction success (i.e.≥ 25%) will be calculated together with a two-sided, 95% CI for the proportion.

The number and proportion of pdVWF switch subjects ABR preservation success will be reported together with the corresponding 95% two-sided CIs for the proportion.

The number and proportion of subjects with categorized spontaneous ABR (i.e. 0, 1-2, 3-5, more than 5 bleeds) will be reported descriptively.

Summary statistics for the total number of infusions, as well as average number of infusions per week will be provided. The total weight adjusted consumption of rVWF (vonicog alfa) during prophylactic treatment will be provided. If applicable, historical data on consumption of pdVWF prior to the study will be summarized as well.

The change in spontaneous ABR from the historical rate to that during the rVWF (vonicog alfa) prophylaxis period will be summarized by location of bleeding (GI, epistaxis, joint bleeding, menorrhagia, oral and other mucosa, muscle and soft tissue, etc.).

13.4.2.2 Pharmacokinetic and Pharmacodynamic Analysis

All PK and PD analyses will use the actual sampling times, not nominal times specified in the protocol, wherever possible. Actual sampling times will be defined as time from the start of infusion to the blood sample collection time. A deviation from the protocol-specified blood sample 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 results were biologically implausible will be eliminated from the analysis.

If any concentration data are considered spurious (e.g. lack of biological plausibility), the reason for exclusion from the analysis and the analysis from which the data point was excluded will be documented.

Details of calculation of PK and PD parameters and corresponding analysis will be given in the statistical analysis plan.

The following PK parameters, based on the initial PK assessment after a washout for on-demand subjects, will be listed and summarized descriptively for VWF:RCo, VWF:Ag and VWF:CB: IR, $T_{1/2}$, MRT, $AUC_{0-\infty}$, $AUC_{0-tlast}$, C_{max}, T_{max}, V_{ss}, and CL. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity, based on the initial PK assessment after a washout for on-demand subjects will be assessed using C_{max}, T_{max}, and $AUC_{0-tlast}$. These PD parameters will be listed and summarized descriptively. PK parameters at steady state ($AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$) for the partial dosing interval will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study for VWF:RCo, VWF:Ag and VWF:CB and summarized descriptively for subjects with the same dosing regimens. The corresponding pharmacodynamics (PD) of rVWF (vonicog alfa) as measured in FVIII activity will be assessed using $AUC_{0-tau;ss}$, $C_{max;ss}$, $T_{max;ss}$, and $C_{min;ss}$. These PD parameters will be listed for on-demand subjects at the end of the study and for switch subjects shortly after reaching steady state and at the end of the study and will be summarized descriptively for subjects with the same dosing regimens.

For the on-demand subjects, the PK of VWF:RCo will be analyzed using a population PK approach to characterize the single and multiple dose pharmacokinetics, including associated variability assessed at after washout and at end of study, respectively. The population PK analysis will be performed in a stepwise manner as outlined below.

1. Exploratory graphical analysis of VWF:RCo versus time data for identification of potential outliers and to inform the pharmacometric analysis.
2. Population PK model development for rVWF (vonicog alfa):
    a. Evaluate alternative structural and stochastic models to describe the typical and individual rVWF (vonicog alfa) profiles.
    b. Investigate and characterize the potential for a time dependency in CL of rVWF (vonicog alfa).
    c. Evaluate, and if necessary refine, the candidate final model

Details of this Population PK analysis will be given in a separate Population PK analysis plan.

For the switch subjects, differences in $AUC_{0\text{-}tau;ss}$, $C_{max;ss}$, and $C_{min;ss}$ assessess shortly after reaching steady state and assessed at the end of the study will be assessed by the ratio of geometric means and corresponding two-sided 95% confidence intervals for VWF:RCo, VWF:Ag,VWF:CB, and FVIII:C. These analyses will be performed using a linear mixed effects model with PK assessment (i.e. factor of two levels relating to the PK assessment shortly after reaching steady state and the PK assessment at end of study, respectively) as a fixed effect and subject as a random effect based on log-transformed PK parameters. 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.

Descriptive statistics will be used to summarize VWF:RCo, VWF:AG and VWF:CB and FVIII:C levels for each nominal time point on the PK curve.

For all subjects in the PKFAS activity/concentration vs. time curves will be prepared.

Formulas for PK parameters IR, $T_{1/2}$, MRT, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}tlast}$, C_{max}, T_{max}, V_{ss}, and CL, $AUC_{0\text{-}tau;ss}$, $C_{max;ss}$, $T_{max;ss}$,and $C_{min;ss}$ will be given in the statistical analysis plan and will be derived using non-compartmental methods in WinNonlin. Analysis of these parameters will be carried out on the PKFAS as well as on the PKPPAS.

13.4.2.3 Safety

Safety analysis will be performed overall and by the two cohorts: on-demand and switch subjects.

TEAEs are defined as AEs with start dates on or after the first exposure to IP. Summaries of AEs will be based on TEAEs unless otherwise indicated.

Occurrence of AEs and SAEs will be summarized descriptively, by system organ class and preferred term. The number and percentage of subjects who experienced AEs and SAEs, and the number of AEs and SAEs will be tabulated. In addition, the number of subjects who experienced AEs assessed as related to IP by the investigator, and the number of IP-related AEs will be tabulated. The number of patients with AEs by severity will be presented similarly.

A listing of all AEs will be presented by subject identifier, age, sex, preferred term and 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.

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 infusion, irrespective of being related or not related to treatment. Temporally associated AEs will be presented in summary tables.

AEs that occurred before first IP infusion will be listed separately.

Adverse events of special interest (AESI), such as hypersensitivity reactions and thromboembolic events, will be monitored throughout the study and statistical analysis will be conducted based on the search criteria (eg, standardised MedDRA queries [SMQ]) determined prior to database lock, and summarized.

For immunogenicity, frequency counts and percentages will be calculated for 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. Clinically significant changes relative to baseline in vital signs and clinical laboratory parameters (hematology, clinical chemistry) will be reported.

13.4.3 Exploratory Outcome Measures

[redacted]

13.4.3.1 [redacted]

[redacted]

13.4.3.2 [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

13.4.3.3 [redacted]

[redacted]

13.4.3.4 [redacted]

[redacted]

13.5 Planned Interim Analysis of the Study

No formal interim analysis is planned for this study.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Trial Agreement (CTA). If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the CTA.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable national and local regulatory requirements as described in the CTA. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

15.1.1 Investigator Report and Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the CTA. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the CTA. Auditing processes specific to the study will be described in the audit plan.

15.5 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. Also, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing whenever pdVWF is used instead of rVWF (vonicog alfa). The reason for this use must also be provided to the sponsor.The sponsor (Baxalta) will also ensure the responsible EC and relevant competent authority are notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.6 Laboratory and Reader Standardization

A central laboratory/reader will be used for all clinical assessments except for pregnancy testing and blood group test (refer to Section 12.9). Local laboratories are requested to provide their laboratory specifications of the individual tests that are also being tested locally.

16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the CTA.

16.2 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the CTA.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

16.3 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients and/or their legally authorized representative must sign an informed consent form before entering into the study according to applicable national and local regulatory requirements and ICH GCP. Before use, the informed consent form will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 16.2). The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable national and local regulatory requirements. Patients or their legally-authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent form, patients or their legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised informed consent form, which have been approved by the applicable EC and regulatory authorities, will be provided by the investigator to the subjects who consented to participate in the study

16.4 Data Monitoring Committee

This study will be monitored by a DMC. The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. 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 stop a trial if it finds toxicities or if treatment is proven to be not beneficial. Details will be defined in the DMC charter.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the CTA.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.7), records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, CRFs, SAERs, laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

If electronic format CRFs are provided by the sponsor, only authorized study site personnel will record or change data on the CRFs. If data is not entered on the CRFs during the study visit the data will be recorded on paper and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (e.g., ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the CTA.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the CTA.

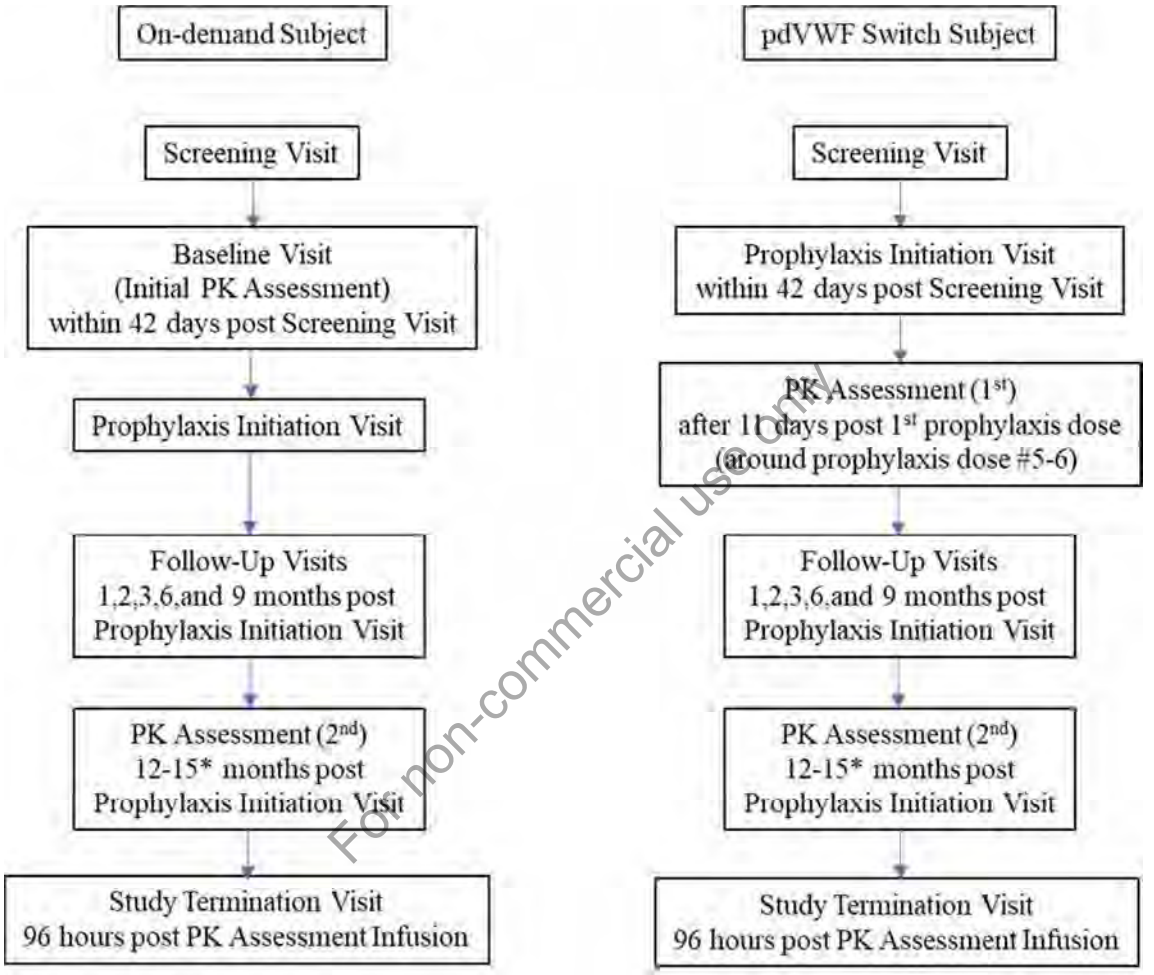
19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the CTA.

20. SUPPLEMENTS

20.1 Study Flow Chart

Figure 1
Study Design for Baxalta Clinical Study 071301



* Study treatment period is extended by 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.

20.2 Schedule of Study Procedures and Assessments

Table 6a
Schedule of Study Procedures and Assessments for On-demand Subject

Procedures/ Assessments	Screening Visit	Baseline Visit (PK-assessment visit)			Prophylaxis Initiation Visit	Interval/Follow-Up Study Visits					PK Assessment at Study Completion			Termination Visit
		Pre-infusion[g]	Infusion	Post-infusion[g]		1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion[g]	Infusion	Post-infusion[g]	Conducted at the 96 hour postinfusion PK Assessment
											12-15[i] month ± 2 weeks			
Informed Consent [a]	X													
Eligibility Criteria	X													
Medical History[b]	X													
Concomitant Medications[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-drug Therapies[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X			X	X	X	X	X	X	X			X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Bleeding Episodes and Treatment and Hemostatic Efficacy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratories	X	X		X	X[h]	X	X	X	X	X	X		X	X
Vital Signs[d]	X	X		X	X	X	X	X	X	X	X		X	X
ECG	X								X					X
IP Treatment[e]			X		X	X	X	X	X	X		X		
IP Consumption / Treatment Compliance						X	X	X	X	X				
Subject Diary					X	X	X	X	X	X				
[redacted]	X[f]								X					X

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[a]) Occurs at enrollment (before screening).
[b]) Including documented history of on-demand treatment for the past 12 months (up to 24 months if available) and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 (up to 24) months.
[c]) Including all medications and non- drug therapies taken in the 2 weeks prior to study entry and all the concomitant medications and non-drug therapies during the course of the study.
[d]) Vital signs: height, weight, body temperature, pulse rate, respiratory rate, and blood pressure. Height is only required at the screening visit. The time points for pre- and post-infusion measurements are (weight is measured pre-infusion only): within 30 minutes before infusion start and 30 ± 15 minutes post-infusion.
[e]) IP treatment after the prophylactic treatment initiation visit at the site will be continued as home-treatment if the subject qualifies; a wash-out period of at least 72 hours is required after the last IP infusion before the follow-up visit. IP infusion will be given at the study site after the blood sample for immunology testing and IR determination is drawn.
[f]) Can be done either at the screening or the baseline visit.
[g]) Time points for PK blood draws: 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 (the 96 hr sampling can be omitted if not allowed by the dosing interval).
[h]) If a subject did not undergo PK assessment, laboratory assessments will be performed at this visit.
[i]) Study treatment period is extended by 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. In this case, 12 month ± 2 weeks visit is to be considered as a follow-up visit, and EOS visit is to be performed once the subject can rollover into the continuation study, from 12 month ± 2 weeks to 15 month ± 2 weeks post prophylaxis initiation visit, as applicable.

Table 6b
Schedule of Study Procedures and Assessments for pdVWF Switch Subject

Procedures/ Assessments	Screening Visit	Prophylaxis Initiation Visit	PK Assessment (at prophylaxis dose #5-6)			Interval/Follow-Up Study Visits					PK Assessment at Study Completion			Termination Visit
			Pre-infusion[g]	Infusion	Post-infusion[g]	1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion[g]	Infusion	Post-infusion[g]	Conducted at the 96 hour postinfusion PK Assessment
											12-15[h] month ± 2 weeks			
Informed Consent [a]	X													
Eligibility Criteria	X													
Medical History[b]	X													
Concomitant Medications[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-drug Therapies[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X	X			X	X	X	X	X	X			X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Bleeding Episodes and Treatment and Hemostatic Efficacy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratories	X	X	X		X	X	X	X	X	X	X		X	X
Vital Signs[d]	X	X	X		X	X	X	X	X	X	X		X	X
ECG	X								X					X
IP Treatment[e]		X		X		X	X	X	X	X		X		
IP Consumption / Treatment Compliance						X	X	X	X	X				
Subject Diary		X				X	X	X	X	X				
[redacted]	X[f]								X					X

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Continued

[a]) Occurs at enrollment (before screening).
[b]) Including documented history of prophylaxis treatment for the past 12 months (up to 24 months if available) and a documented history, e.g., patient charts and prescription information, of all bleeding episodes within the past 12 (up to 24) months.
[c]) Including all medications and non- drug therapies taken in the 2 weeks prior to study entry and all the concomitant medications and non-drug therapies during the course of the study.
[d]) Vital signs: height, weight, body temperature, pulse rate, respiratory rate, and blood pressure. Height is only required at the screening visit. The time points for pre- and post-infusion measurements are (weight is measured pre-infusion only): within 30 minutes before infusion start and 30 ± 15 minutes post-infusion.
[e]) IP treatment after the prophylactic treatment initiation visit at the site will be continued as home-treatment if the subject qualifies; a wash-out period of at least 72 hours is required after the last IP infusion before the follow-up visit. IP infusion will be given at the study site after the blood sample for immunology testing and IR determination is drawn.
[f]) Can be done either at the screening or the prophylaxis initiation visit.
[g]) Time points for PK blood draws: 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 (the 96 hr sampling can be omitted if not allowed by the dosing interval).
[h]) Study treatment period is extended by 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. In this case, 12 month ± 2 weeks visit is to be considered as a follow-up visit, and EOS visit is to be performed once the subject can rollover into the continuation study, from 12 month ± 2 weeks to 15 month ± 2 weeks post prophylaxis initiation visit, as applicable.

20.2.1 Summary Schedule of Visit Assesments for Surgical Bleeding

Table 7
Summary Schedule of Visit Assessments for Surgical Bleeding

Procedures/ Assessments	**Surgical procedure**				**Post-Operative Day 7 Visit (± 1 day)**	**Post-Operative Day 14 Visit (± 2 day)**
	Priming Dose Procedures (12-24 hours prior to surgery)	**Loading Dose Procedures (≤ 3 hours prior to surgery)**	**Intraoperative**	**Postoperative (day 1 → end of perioperative IP treatment)[a]**		
ECG						X
Physical examination[b]	X	X		X	X	X
Adverse events	X	X	X	X	X	X
Laboratories[c]	X	X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X
IP treatment: rVWF (vonicog alfa):ADVATE (rFVIII, octocog alfa) or rVWF (vonicog alfa) only infusion	X	X	X as required	X as required	X as required	X as required
Concomitant medications and non-drug therapy	X	X	X	X	X	X
[redacted]						X
Hemostatic efficacy assessments[e]			X	X	X	X
Blood loss		X estimated	X actual	X	X[f]	X[f]
Treatment days estimate		X				

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Continued

[a)] The assessments will be performed daily until perioperative IP treatment end (potentially multi-visits)
[b)] Physical Examination: within 2 hours prior to IP infusion start
[c)] For laboratory assessments, see Table 9
[d)] Vital signs: within 30 minutes before infusion start and 30 ± 15 minutes post-infusion
[e)] Completed immediately postsurgery by the operating surgeon 24 hours post last IP infusion or at Day 14 visit (whichever occurs first) by the investigator
[f)] In case bleeding still ongoing

20.3 Clinical Laboratory Assessments

Table 8a
Clinical Laboratory Assessments for On-demand Subject

Procedures/ Assessments	Screening Visit	Baseline Visit (PK-assessment visit)			Prophylaxis Initiation Visit[k]	Interval/Follow-Up Study Visits					PK Assessment[m] at Study Completion			Termination Visit
		Pre-infusion	Infusion	Post-infusion		1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion	Infusion	Post-infusion	Conducted at the 96 hour postinfusion PK Assessment
											12-15[n] month± 2 weeks			
Hematology [a]	X	X		X	X	X	X	X	X	X	X		X	X
Clinical Chemistry[b]	X	X		X	X	X	X	X	X	X	X		X	X
Coagulation Panel/ PK assessment[c]	X	X		X	X	X	X	X	X	X	X		X	
Immunogenicity[d]	X	X			X[l]	X	X	X	X	X	X			X
Viral Serology[e]	X													
Urinalysis[f]	X													
VWD Gene Mutational Analysis / HLA genotype analysis and Analysis of VWF multimers[g]	X													
sP-selectin and D-dimer	X[h]													
Blood Group[i]	X													
Pregnancy Test[j]	X													

[a)] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. Hematology assessments during PK assessments will be determined prior to IP infusion and 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours thereafter. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

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[b)] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin. Clinical chemistry will be determined prior to IP infusion and after 24 ± 2 h, 48 ± 2 hours and 72 ± 2 hours during the PK assessments. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

[c)] Coagulation panel/PK assessment (also refers to IR pre/post dose assessments at prophy initiation visit and each follow-up visit): PT, INR and aPTT (only for screening), VWF:RCo, VWF:Ag, VWF:CB, FVIII:C,; during the PK assessment at the baseline visit blood samples will be drawn 30 min prior PK infusion; once the PK infusion is completed 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 and VWF:RCo, VWF:CB, VWF:Ag, FVIII:C will be determined; for follow-up visits, IR samples will be drawn within 30 minutes pre-infusion and 30 ± 5 minutes post-infusion. During screening and in case of thromboembolic event VWF multimers and ADAMTS13 will be analyzed to judge on a possibly relatedness to UHMW fractions of the IP.

[d)] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII –Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG . In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined. For on-demand subjects, a washout period of at least 72 hours after the last IP infusion is required before blood samples for immunogenicity assessments can be drawn.

[e)] Viral Serology 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; HIV-1/HIV-2 Antibodies

[f)] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH

[g)] Not required if available in the subject's medical history; VWF multimers: additionally in case of thromboembolic events

[h)] At screening and in case of thromboembolic events

[i)] Blood group assessment major blood group (local laboratory) only if not available in the subject's medical history

[j)] Serum pregnancy test (in females of child-bearing potential if no urine sample is available)

[k)] The last post-infusion laboratory assessments coincidence with the initiation visit for prophylactic treatment. After the blood samples are drawn for laboratory assessment for the 96 h post infusion PK assessment, the subject receives the first IP infusion for prophylactic treatment (prophylactic treatment initiation visit).

[l)] Only needed for subjects without PK assessment prior to their first IP infusion in this study.

[m)] A steady state full PK analysis will be performed at the end of the study. 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), the 96 hr sampling can be omitted if not allowed by the dosinig interval.

[n)] Study treatment period is extended by 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. In this case, 12 month ± 2 weeks visit is to be considered as a follow-up visit, and EOS visit is to be performed once the subject can rollover into the continuation study, from 12 month ± 2 weeks to 15 month ± 2 weeks post prophylaxis initiation visit, as applicable.

Table 8b
Clinical Laboratory Assessments for pdVWF Switch Subject

Procedures/ Assessments	Screening Visit	Prophylaxis Initiation Visit	PK Assessment[k] (at prophylaxis dose #5-6)			Interval/Follow-Up Study Visits					PK Assessment[k] at Study Completion			Termination Visit
			Pre-infusion	Infusion	Post-infusion	1 month ± 1 week	2 month ± 1 week	3 month ± 2 weeks	6 month ± 2 weeks	9 month ± 2 weeks	Pre-infusion	Infusion	Post-infusion	Conducted at the 96 hour postinfusion PK Assessment
											12-15[l] month± 2 weeks			
Hematology [a]	X	X	X		X	X	X	X	X	X	X		X	X
Clinical Chemistry[b]	X	X	X		X	X	X	X	X	X	X		X	X
Coagulation Panel/PK assessment[c]	X	X	X		X	X	X	X	X	X	X		X	
Immunogenicity[d]	X	X				X	X	X	X	X	X			X
Viral Serology[e]	X													
Urinalysis[f]	X													
VWD Gene Mutational Analysis / HLA genotype analysis and Analysis of VWF multimers[g]	X													
sP-selectin and D-dimer	X[h]													
Blood Group[i]	X													
Pregnancy Test[j]	X													

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[a)] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. Hematology assessments during PK assessments will be determined prior to IP infusion and 24 ± 2 hours, 48 ± 2 hours and 72 ± 2 hours thereafter. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

[b)] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin. Clinical chemistry will be determined prior to IP infusion and after 24 ± 2 h, 48 ± 2 hours and 72 ± 2 hours during the PK assessments. For other IP-associated visits, samplings are within 60 minutes pre-infusion.

[c)] Coagulation panel/PK assessment (also refers to IR pre/post dose assessments at prophy initiation visit and each follow-up visit): PT, INR and aPTT (only for screening), VWF:RCo, VWF:Ag, VWF:CB, FVIII:C,; during the PK assessment blood samples will be drawn 30 min prior PK infusion; once the PK infusion is completed 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 and VWF:RCo, VWF:CB, VWF:Ag, FVIII:C will be determined; for follow-up visits, IR samples will be drawn within 30 minutes pre-infusion and 30 ± 5 minutes post-infusion. During screening and in case of thromboembolic event VWF multimers and ADAMTS13 will be analyzed to judge on a possibly relatedness to UHMW fractions of the IP.

[d)] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII –Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG. In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined. For switch subjects, the wash out period may be reduced to the time interval between their pdVWF prophy infusions.

[e)] Viral Serology 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; HIV-1/HIV-2 Antibodies

[f)] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH

[g)] Not required if available in the subject's medical history; VWF multimers: additionally in case of thromboembolic events

[h)] At screening and in case of thromboembolic events

[i)] Blood group assessment major blood group (local laboratory) only if not available in the subject's medical history

[j)] Serum pregnancy test (in females of child-bearing potential if no urine sample is available)

[k)] A full steady state PK analysis will be performed. 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) , the 96 hr sampling can be omitted if not allowed by the dosinig interval.

[l)] Study treatment period is extended by 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. In this case, 12 month ± 2 weeks visit is to be considered as a follow-up visit, and EOS visit is to be performed once the subject can rollover into the continuation study, from 12 month ± 2 weeks to 15 month ± 2 weeks post prophylaxis initiation visit, as applicable.

20.3.1 Laboratory Sampling for Surgical Bleeding

Table 9
Laboratory Sampling[a] for Surgical Bleeding

Procedures/ Assessments	**Surgical procedure**				**Post-Operative Day 7 Visit (± 1 day)**	**Post-Operative Day 14 Visit (± 2 day)**
	Priming Dose Procedures (12-24 hours prior to surgery)	**Loading Dose Procedures (≤ 3 hours prior to surgery)**	**Intraoperative**	**Postoperative (day 1 → end of perioperative IP treatment)[b]**		
Hematology[c]	X (w/o Differential)	X[d] (w/o Differential)		X (w/o Differential)	X	X
Clinical Chemistry[e]	X	X[d]			X	X
Coagulation panel[f]	X	X	X	X	X	X
VWF inhibitory and binding antibodies, antibodies to other proteins[g]	X	X	X if excessive or unexplainedbleeding	X	X	X
Urinalysis[h]					X	X
VWF Multimers[i]						
Anti VWF IgE antibody testing only in case of allergic reaction/ anaphylaxis						

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Continued

[a)] Blood draws are within 3 hrs prior to infusion start, expect that for the priming dose blood draw is within 30 minutes prior to infusion start. For coagulation panel, an additional 30 ± 5 minutes post-infusion blood draw is needed.
[b)] The assessments will be performed daily until perioperative IP treatment end (potentially multi-visits)
[c)] Hematology assessments include: complete blood count [hemoglobin, hematocrit, erythrocytes (i.e. red blood cell count), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e. white blood cell count)] with differential (i.e. basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.
[d)] Not required if sample already drawn at the time of the priming dose
[e)] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (AP), bilirubin.
[f)] Coagulation panel: VWF:RCo, VWF:Ag, FVIII:C PT INR and aPTT; in additiona to pre-infusion, 30 ± 5 minutes post infusion blood draw is needed.
[g)] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to FVIII – Neutralizing and Neutralizing Ab to VWF:RCo, Neutralizing Ab to VWF:CB, Neutralizing Ab to VWF:FVIII, Binding Ab to VWF and FVIII, Binding Ab to CHO-Protein, Binding Ab to rFurin, Binding Ab to Murine IgG. In case of an SAE hypersensitivity reaction IgE antibodies to VWF will be determined.
[h)] Urinalysis comprehends: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH
[i)] VWD multimers and ADAMTS13 during the study only in case of thrombotic events

20.4 Contraceptive Methods for Female Subjects of Childbearing Potential

In this study, subjects who are women of childbearing potential must agree to utilize a highly effective contraceptive measure throughout the course of the study and for 30 days after the last administration ofIP. In accordance with the Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials (version 2014-09-15)[ii], birth control methods which may be considered as highly effective include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable[iii]
- Intrauterine device (IUD)[iii]
- Intrauterine hormone-releasing system (IUS) [iii]
- Bilateral tubal occlusion[iii]
- Vasectomised partner(s)[iii]
- Sexual abstinence during the entire study period

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

[ii] Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf.

[iii] Contraception methods that are considered to have low user dependency.

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19. [redacted]

20. [redacted]

21. [redacted]

22. SUMMARY OF CHANGES

Protocol 071301: Local Amendment 11 (Russia): 2019 JAN 28

Replaces: Global Amendment 6: 2018 MAR 12

In this section, changes from the previous version of the Protocol, dated 2018 MAR 12, are described and their rationale is given.

1. **Throughout the document**
   Description of Change:
   Minor grammatical and/or administrative changes and/or rewording have been made.
   Purpose for Change: To improve the readability and/or clarity of the protocol.

2. **Synopsis (Study Design), Section 8.1**
   Description of Change:
   Added the wording about the possible up-to 3 months' extension of study participation for certain subjects.
   Purpose for Change: To add information about possible extension of study participation for certain subjects.

3. **Synopsis (Planned Duration of Subject Participation), Section 8.**2
   Description of Change:
   Added the note about the possible up-to 3 months' extension of study participation for certain subjects, and clarify that the planned duration of subject participation can therefore be extended to 18 months.
   Purpose for Change: To add information about possible extension of study participation for certain subjects.

4. **Synopsis (Secondary outcome measures), Section 8.3.2.1**
   Description of Change:
   Original text:
   Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 bleeding episodes during the 12-month prophylactic treatment with rVWF (vonicog alfa)
   New text:
   Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 bleeding episodes during the prophylactic treatment with rVWF (vonicog alfa)
   Purpose for Change: To remove the exact prophylactic treatment period as it can be extended beyond 12 month for certain subjects.

5. **Section 6.1**

Description of Change:
Updates were added to reflect the marketing authorization for Vonvendi/Veyvondi in US, EU, Switzerland and Canada.
Purpose for Change: To provide updated marketing authorization for Vonvendi/Veyvondi.

6. **Section 10.3.7**

Description of Change:
The detailed schedules of follow-up visits were removed as for certain subjects 12-month follow-up visit will be scheduled with the need of participation extension.
Purpose for Change: To remove the details to avoid confusion of possible 12-month follow-up visit.

7. **Section 10.3.9**

Description of Change:
End of study visit time was removed as for certain subjects the EOS visit can occur after 12 months with the need of participation extension.
Added the note about the possible up-to 3 months' extension of study participation for certain subjects.
Purpose for Change: To add information about possible extension of study participation for certain subjects and to remove the details to avoid confusion of possible delayed EOS visit.

8. **Section 11.6, Section 12.10.2**

Description of Change:
Added the note about the possible up-to 3 months' extension of study participation for certain subjects.
Purpose for Change: To add information about possible extension of study participation for certain subjects.

9. **Section 20.2 Table 6a 6b, Section 20.3 Table 8a 8b**

Description of Change:
Added the footnote to reflect the possible up-to 3 months' extension of study participation for certain subjects.
Purpose for Change: To add note about possible extension of study participation for certain subjects.

10. **Section 20.2 Table 6a 6b, Section 20.3 Table 8a 8b**
Description of Change:
Some clarifications were made to the tables and the footnotes, to reflect the possible up-to 3 months' extension of study participation for certain subjects.
Purpose for Change: To add information about possible extension of study participation for certain subjects.

INVESTIGATOR ACKNOWLEDGEMENT

RECOMBINANT VON WILLEBRAND FACTOR (rVWF)

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

CLINICAL TRIAL PHASE 3

LOCAL AMENDMENT 11 (RUSSIA): 2019 JAN 28

Replaces: GLOBAL AMENDMENT 6: 2018 MAR 12

OTHER PROTOCOL ID(s)
NCT Number: NCT02973087
EudraCT Number: 2016-001478-14
IND NUMBER: 013657

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT

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Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
[redacted], MD
[redacted]
Global Clinical Development Operations
Baxalta Innovations GmbH