Clinical Study Protocol

NCT Number: NCT03879135

Title: A Phase 3b, Prospective, Open-Label, Uncontrolled, Multicenter Study on Long-Term Safety and Efficacy of rVWF in Pediatric and Adult Subjects With Severe Von Willebrand Disease (VWD)

Study Number: SHP677-304

Document Version and Date: Amendment 4, 20 Dec 2021

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

PROTOCOL: SHP677-304

TITLE:	A PHASE 3B, PROSPECTIVE, OPEN-LABEL, UNCONTROLLED, MULTICENTER STUDY ON LONG-TERM SAFETY AND EFFICACY OF rVWF IN PEDIATRIC AND ADULT SUBJECTS WITH SEVERE VON WILLEBRAND DISEASE (VWD)
SHORT TITLE:	rVWF Pediatric and Adult Study
STUDY PHASE:	Phase 3b
DRUG:	Recombinant von Willebrand factor (rVWF, vonicog alfa)
IND NUMBER:	013657
EUDRACT NUMBER:	2018-003453-16
SPONSOR:	Takeda Development Center Americas, Inc.* 95 Hayden Avenue, Lexington, MA 02421 USA and Baxalta Innovations GmbH** Industriestrasse 67, A-1221 Vienna, AUSTRIA * Formerly Baxalta and later Shire ** Baxalta is now part of Takeda
PRINCIPAL/ COORDINATING INVESTIGATOR:	Multicenter
PROTOCOL HISTORY:	**Amendment 4: 20 DEC 2021** Replaces: Amendment 3: 19 MAY 2020 Amendment 1: 29 MAY 2019 Original Protocol: 29 AUG 2018 (Amendment 2: 08 JUL 2019 did not take effect)

PROTOCOL SIGNATURE PAGE

Sponsor's (Takeda) Approval

Signature:	[redacted]
[redacted] MD, PhD, MS [redacted] Rare Diseases Therapeutic Area Unit, Takeda Development Center Americas, Inc.	

Investigator's Acknowledgement

I have read this protocol (version: Amendment 4) for Study SHP677-304.

Title: A phase 3b, prospective, open-label, uncontrolled, multicenter study on long-term safety and efficacy of rVWF in pediatric and adult subjects with severe von Willebrand disease (VWD)

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please handprint or type)	

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS PROTOCOL VERSION

Protocol Amendments		
Summary of Change(s) from Amendment 1 Version of Approved Protocol		
Amendment Number 4	**Amendment Date 20 DEC 2021**	**Global**
Description of Change		**Section(s) Affected by Change**
Update of Sponsor to Takeda Development Center Americas, Inc.		Throughout the document
Procedures for Safety Reporting and Product Quality Complaints have been updated based on the change in sponsor.		Emergency Contact Information Product Quality Complaints Appendix 3.4 Appendix 3.5 Appendix 3.8
Minor grammatical and administrative changes, rewording and updates to abbreviations have been made for consistency, to remove redundancies, and to improve the readability and clarity of the protocol.		Throughout the document
Protocol Signature Page has been updated to reflect current sponsor signatory		Protocol Signature Page
The minimum number of 5 subjects with type 3 VWD on prophylactic regimen to be included in the sample population are required to be newly enrolled. The total sample size has been updated to include up to 71 pediatric and adult subjects: up to 22 adult subjects transitioning from Study 071301; up to 34 pediatric/adolescent subjects transitioning from Study 071102; and, for Cohort 4, "at least 7 up to 15" newly enrolled adult and pediatric/adolescent subjects.		Section 1.1 – Number of Subjects Section 2.4 Section 9.3
An end-of-study pharmacokinetic/pharmacodynamic assessment has been added for Cohorts 1, 2, 3, and 4.		Section 1.1 – PK Assessment, Pharmacokinetic Endpoints, Analysis of Exploratory Outcome Measures - Pharmacokinetics and Pharmacodynamics Section 1.3 Section 3.2 Section 6.2.2.4 Section 8.3.6 Section 8.4.4 Section 9.7.1
The rationale for the sample size has been clarified.		Section 1.1 – Number of Subjects (Total and per Treatment Arm)
The planned study end date has been extended to December 2025. The time for completion of the study has been extended.		Section 1.1 – Study Period (Planned) Section 4.4

Protocol Amendments		
Summary of Change(s) from Amendment 1 Version of Approved Protocol		
Amendment Number 4	**Amendment Date 20 DEC 2021**	**Global**
Description of Change		**Section(s) Affected by Change**
The analysis of the primary endpoint has been specified as the number of spontaneous (assessed by investigator) bleeds requiring treatment with a VWF product.		Section 1.1 – Statistical Analysis – Analysis of Primary Endpoint Section 9.5.1
Methods of summarization of spontaneous ABR have been specified.		Section 1.1 – Efficacy of Prophylaxis Section 9.5.1 Section 9.5.2.1
The relationship of the end of study visit of the parent study and the screening visit of this study has been clarified.		Section 1.3 Section 8.1
The frequency of measurement of binding antibodies to Chinese hamster ovary protein, rFurin, and murine IgG has been decreased.		Section 1.3
The requirement for subjects to use the e-diary and to inform the site/Investigator and follow instructions if problems occurred with the e-diary have been emphasized. E-diary procedures have been made consistent throughout the protocol.		Section 1.3 Section 8.3.1 Section 8.3.9
The requirement to draw blood samples for pre-infusion testing has been reduced to pre-infusion only after the 12-month visit.		Section 1.3
A more specific explanation of the differences between pdVWF and rVWF has been added. Additional information about approval of Vonvendi has been added.		Section 2.2
Study 071301 has been moved to the list of completed studies and removed from the list of ongoing studies.		Section 2.2.2.1 Section 2.2.2.2
Language describing re-evaluation of dosing for subjects transitioning from Study 071301 and Study 071102 to this continuation study has been adjusted to reflect that rollover of subjects from these studies to this continuation study is complete.		Section 4.1
Consultation with study medical monitors has been required to assess whether pediatric subjects could receive IP for peri-operative management of bleeding if they need surgery while participating in this study.		Section 4.1

Protocol Amendments		
Summary of Change(s) from Amendment 1 Version of Approved Protocol		
Amendment Number 4	**Amendment Date 20 DEC 2021**	**Global**
Description of Change		**Section(s) Affected by Change**
Additional measures and procedures have been added to protect participant safety and to ensure the integrity of the clinical trial, as a result of the COVID-19 pandemic.		Section 4.8 Section 6.2.2.1.2 Section 6.2.2.2.1 Section 7.2 Section 8.3 Section 8.3.1 Section 9.1 Appendix 1.2 Appendix 1.4 Appendix 1.5 Appendix 2 Appendix 3.3
The use of partial vials has been allowed for pediatric subjects to prevent exceeding the dose range recommended per protocol.		Section 6.2
A clarification has been made that ADVATE is to be used if/when needed to treat bleeding episodes.		Section 6.2 Section 8.4.2.3
The target level of FVIII:C has been specified as >0.3 IU/mL (30%) for choosing an initial rVWF dose for the treatment of bleeding episodes. The target level of endogenous FVIII has been specified as at least 30 IU/dL for the rVWF priming dose for minor or oral surgery.		Section 6.2.2.2 Section 6.2.2.3
Emphasis has been added that, especially for pediatric subjects, rounding to the nearest vial size should be avoided.		Section 6.2.2.2
New subjects screened for eligibility for Cohort 4 who experience bleeding episodes requiring treatment with VWF before the prophylaxis initiation visit are to be treated with the subject's standard of care. Cohort 4 subjects are also to have a washout period of at least 5 days prior to rVWF PK infusion at the PK assessment visit.		Section 6.2.2.2.1 Section 8.3.1
Pediatric and adolescent subjects who require surgical, invasive, or oral/dental procedures while participating in this study have been allowed to receive IP (rVWF) to manage surgery/procedure related bleeding if their corresponding age cohort in Study 071102 has been opened to allow enrollment of subjects for the type of surgery/procedure required in this study.		Section 6.2.2.3
A clarification has been made that new subjects are ineligible for the study if they are scheduled for surgical intervention at the time of screening for Cohort 4.		Section 6.2.2.3
IP administration procedures have been modified to allow subjects qualified for home treatment to receive IP from a healthcare professional trained and qualified trained and qualified by the site investigator.		Section 6.5

Protocol Amendments		
Summary of Change(s) from Amendment 1 Version of Approved Protocol		
Amendment Number 4	**Amendment Date 20 DEC 2021**	**Global**
Description of Change		**Section(s) Affected by Change**
A pre-screening medical evaluation has been added.		Section 8.3.1
Multimer analysis and VWD gene mutation analysis have been permitted to be performed as soon as possible during the subject's participation in the study, if they cannot be performed at screening and the subject meets all eligibility criteria.		Section 8.3.1
The timing of the prophylaxis initiation visit has been clarified.		Section 8.3.1 Section 8.3.3
The timing of scheduling of follow-up visits and immunogenicity assessments has been clarified.		Section 8.3.4
Procedures to be performed at unscheduled visits that replace missed scheduled follow-up visits have been clarified.		Section 8.3.5
A definition has been provided for subjects considered to have completed study treatment.		Section 8.3.6
More detailed instructions have been provided for the assessment of hemostatic efficacy for the treatment of bleeding episodes.		Section 8.4.2.4
"Hypersensitivity reaction" has been changed to "anaphylactic reaction."		Section 8.4.3.3
Directions for recording COVID-19 vaccination have been added.		Section 8.4.3.7
The conditions under which local laboratory testing may be used have been specified, and a requirement has been added to draw a back-up sample for confirmatory testing at the central laboratory.		Section 8.4.3.11.1
The number of healthy plasma donors included in the negative control for the anti-VWF antibody assay has been modified		Section 8.4.3.13.1.2
The assessment of the impact of VWD on subject health has been modified to include the number of days missed from school or work.		Section 8.4.5.3
The definition of spontaneous annualized bleeding rate in the primary efficacy endpoint has been clarified as spontaneous bleeds as assessed by the investigator and requiring treatment with a VWF product during the first 12 months of study treatment.		Section 9.5.1
Postmarketing adverse drug reactions have been added.		Appendix 3.12

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the "Takeda Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol" within 24 hours to Takeda Global Patient Safety Evaluation (GPSE). The fax number and e-mail address are provided on the form (sent under separate cover). A copy of this form must also be sent to the contract research organization (CRO)/Takeda medical monitor using the details below.

For protocol- or safety-related questions or concerns <u>during normal business hours</u> 9:00 AM through 5:00 PM EST (North America), the investigator must contact the medical monitor:

Takeda Medical Monitor:
[redacted], MD, PhD
Mobile: [redacted]
Email: [redacted]

IQVIA medical monitor:
[redacted], Jr, MD, MS
Mobile: [redacted]
Fax: [redacted]
Email: [redacted]

For protocol- or safety-related questions or concerns <u>outside of normal business hours</u>, the investigator must contact the 24-hour hotline:

For 24-hour urgent medical contact: contact on mobile phone, or at the following numbers:
US primary +1 512 652 0191
US alternate +1 512 652 0864
EU +33 186 990 019

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or non-medical complaints to Takeda within 24 hours. If requested, defective product(s) will be returned to the sponsor for inspection and analysis.

A product quality complaint includes any instances where there is an allegation or report relating to Takeda licensed or investigational products, received in writing, electronically, or orally, which indicates an impact to a product's strength, identity, safety, purity, or quality, or which suggests that a product did not meet the criteria defined in the regulatory applications, licenses, or marketing authorizations for the product. Examples of investigational product quality complaints include, but are not limited to, the following:

Unit issues	• Capsule fill empty or overage • Bottle/vial fill shortage or overage • Capsule/tablet damaged/broken • Syringe/vial cracked/broken	• Syringe leakage • Missing components • Product discoloration • Device malfunction
Labeling	• Label missing • Leaflet or Instructions For Use (IFU) missing • Label illegible	• Incomplete, inaccurate, or misleading labeling • Lot number or serial number missing
Packaging	• Damaged packaging (e.g., secondary, primary, bag/pouch) • Tampered seals • Inadequate or faulty closure	• Missing components within package
Foreign material	• Contaminated product • Particulate in bottle/vial • Particulate in packaging	

Please report the product quality complaint using the "Product Quality Complaint Data Collection Form" via the email address:

ctmcomplaint@takeda.com

Telephone number (provided for reference if needed):
Takeda, Lexington, MA (USA)
1-800-828-2088

For instructions on reporting adverse events (AEs) related to product complaints, see Appendix 3.4.

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1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol number: SHP677-304	**Drug:** Recombinant von Willebrand factor (rVWF, vonicog alfa)
Title of the study: A phase 3b, prospective, open-label, uncontrolled, multicenter study on long-term safety and efficacy of rVWF in pediatric and adult subjects with severe von Willebrand disease (VWD)	
Short title: rVWF Pediatric and Adult Study	
Study phase: Phase 3b	
Number of subjects (total and per treatment arm): Up to 71 pediatric and adult subjects with severe VWD (including at least 5 newly enrolled subjects with type 3 VWD on prophylactic regimen) will be included, composed of: a) up to 22 adult subjects transitioning from Study 071301; b) up to 34 pediatric subjects transitioning from Study 071102; c) at least 7 up to 15 newly enrolled adult (aged ≥18 years) and pediatric/adolescent (aged 12 to <18 years) subjects who have been receiving VWF products for on-demand (OD) treatment. The number of subjects in this study is primarily driven by the number of subjects who could transition from the 2 parent studies, 071301 and 071102, as well as practical considerations and the EMA Guideline on the Clinical Investigation of Human Plasma Derived von Willebrand Factor Products (CPMP/BPWG/220/02). Sample size is not based on a power calculation for a significance test.	
Investigator(s): Multicenter Study	
Site(s) and Region(s): The study will be conducted at approximately 55 study sites in the United States, Canada, Turkey, Russian Federation, Ukraine, and European Union (EU).	
Study period (planned): Dec 2018 to Dec 2025	**Clinical phase:** 3b
Objectives: **Primary:** • To evaluate the efficacy of rVWF (vonicog alfa) prophylaxis based on the annualized bleeding rate (ABR) of spontaneous (not related to trauma) bleeding episodes in adult (aged ≥18 years) and pediatric/adolescent (aged 12 to <18 years) subjects during the first 12 months on study treatment. **Secondary:** • To evaluate the long-term safety of rVWF (vonicog alfa) in adult and pediatric subjects as assessed by adverse events (AEs) including thrombogenicity, hypersensitivity, and immunogenicity, as well as by vital signs and clinical laboratory parameters • To evaluate the efficacy of rVWF (vonicog alfa) prophylaxis in adult and pediatric/adolescent subjects while enrolled in the study • To evaluate the efficacy of different dose regimens for prophylactic treatment in adult and pediatric/adolescent subjects • To assess the efficacy of rVWF (vonicog alfa) for OD treatment of bleeding episodes (spontaneous and	

traumatic) in adult and pediatric subjects

Exploratory

In adult and pediatric subjects treated with rVWF (vonicog alfa):

- To obtain additional data on the efficacy of perioperative bleeding management with rVWF (vonicog alfa) if surgery is required
- To assess pharmacokinetics (PK) and pharmacodynamics (PD) of rVWF (vonicog alfa) and to monitor incremental recovery of rVWF (vonicog alfa) over time in adult and pediatric subjects
- To assess health-related Quality of Life (HRQoL) data, treatment satisfaction and health resource utilization over time for subjects receiving rVWF (vonicog alfa) prophylaxis

Rationale:

To evaluate the long-term safety and hemostatic efficacy of rVWF (vonicog alfa) prophylaxis in adult and pediatric/adolescent (aged 12 to <18 years) subjects with severe VWD with the option of once weekly dosing, and to further assess the safety and efficacy of rVWF in OD treatment of bleeding episodes, and in perioperative management of surgical bleeding in adult and pediatric subjects of all ages with severe VWD.

Investigational product, dose, and mode of administration:

Recombinant von Willebrand factor (rVWF, vonicog alfa) is administered intravenously.

Prophylactic Treatment

a. **Cohort 1**: Adult subjects from Study 071301 who will continue with the same prophylactic treatment regimen from Study 071301, which is expected to be 50 (±10) IU/kg recombinant von Willebrand factor: Ristocetin cofactor (rVWF:RCo) twice weekly for the majority of subjects.
b. **Cohort 2**: Adult subjects from Study 071301 who experienced no clinically significant bleeding episode over the past 6 months and who elected to follow the recommendation by the investigator to start prophylactic treatment in this study with reduced dosing frequency and/or change of dose per infusion.
c. **Cohort 3**: Pediatric/adolescent subjects aged 12 to <18 years who:
    - transition from Study 071102 with at least 3 bleeding episodes (not including menorrhagia) that required treatment with a VWF product and occurred over the past 12 months, and
    - are considered eligible for prophylactic treatment per investigator's medical/clinical assessment

    may receive rVWF (vonicog alfa) for prophylaxis if they elect to go on prophylactic treatment following the recommendation by the investigator.

    The dosage selected may be either:
    a) Twice weekly 50 (±10) IU/kg rVWF:RCo, or
    b) Once weekly 50 (±10) IU/kg rVWF:RCo

    based on the investigator's assessment and recommendation.
    Dosage may be individualized within this range and, in consultation with the sponsor, increased up to 80 IU/kg if considered necessary to assure effective prophylaxis, based on:

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

d. **Cohort 4:** Newly enrolled adult and pediatric/adolescent (aged 12 to <18 years) subjects who:

- were previously treated with VWF products for bleeding episodes OD, with at least 3 bleeding episodes (BE), excluding menorrhagia, that occurred over the past 12 months, and
- are considered eligible for prophylactic treatment based on the investigator's medical/clinical assessment

will receive rVWF (vonicog alfa) at once weekly dose of 50 (±10) IU/kg rVWF:RCo. Dosage may be individualized within this range and, in consultation with the sponsor, increased up to 80 IU/kg if considered necessary to assure effective prophylaxis, based on:

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

For all subjects on prophylaxis, dose and/or dose frequency will be increased based on bleeding episode dose-escalation criteria. Dose escalations (not exceeding the upper limit of 80 IU/kg rVWF:RCo per dose) and/or increase of dose frequency will only be allowed in case of insufficient therapeutic response with breakthrough bleeding episodes. The criteria for dose and/or dose frequency escalation are specific to each bleeding location but, in general, involve 1 significant breakthrough bleeding episode despite the subject being compliant with scheduled prophylactic treatment. For subjects who require a dose escalation due to a breakthrough bleed, the frequency should preferentially be kept the same but the dose (IU VWF:RCo per infusion) should be increased up to 80 IU VWF:RCo. Based on the subject's bleeding history, investigator's clinical judgement and the pharmacokinetic data (if available), dose escalation by increasing the dose frequency should be considered. Changes in dose or dose frequency should only be done in consultation with the Sponsor. (For details on dose escalation, please refer to protocol Section 6.2.2.1.2.)

Treatment of Bleeding Episodes

Cohort 5: will consist of pediatric subjects of all ages (aged <18 years) from Study 071102 who are considered not eligible for prophylactic treatment based on the investigator's medical/clinical assessment or who elect not to follow the recommendation by the investigator to transition to prophylaxis

Cohort 6: will consist of adult subjects from Study 071301 who are considered by the principal investigator (PI) as medically more suitable for OD treatment or who prefer to switch back to OD treatment regimen

Dosage and frequency must be individualized based on the subject's weight, VWD type and severity of bleeding episode and monitoring of appropriate clinical and laboratory measures. In general, an initial dose of 40 to 60 IU/kg VWF:RCo is recommended. Depending on the subject's baseline factor VIII (FVIII) level, rVWF should be given with or without 30 to 45 IU/kg ADVATE (rFVIII, octocog alfa) (rVWF: rFVIII ratio of 1.3± 0.2:1). The rFVIII dose should be calculated according to the difference between the subject´s baseline plasma FVIII clotting activity (FVIII:C), and the desired peak FVIII:C level to achieve appropriate plasma FVIII:C level. In cases of major bleeding episodes, a dose of up to 80 IU/kg VWF:RCo may be infused. If necessary, subsequent doses of 40 to 60 IU/kg VWF:RCo will be administered every 8 to 24 hours with or without ADVATE [rFVIII, octocog alfa] (only to be administered if plasma FVIII levels fall below 30 IU/dL during the treatment period) to maintain VWF:RCo and FVIII levels for as long as deemed necessary by the investigator.

Management of Perioperative Bleeding

The dose and frequency of administration of rVWF will be individualized based on the type of surgery, PK results, and VWF and FVIII levels. In general, the dose will be tailored to raise the VWF:RCo concentration to 100% of normal for major surgeries, and to 50% to 60% of normal for minor and oral surgeries.

For subjects undergoing elective surgery, an rVWF priming dose is to be infused 12 to 24 hours prior to surgery in subjects with inadequate levels of FVIII, to allow the endogenous FVIII levels to increase to at least 30 IU/dL (for minor and oral surgery) or 60 IU/dL (for major surgery) before the loading dose of rVWF (vonicog alfa).

For both elective and emergency surgery, an rVWF loading dose should be administered within 3 hours prior to surgery. ADVATE (rFVIII, octocog alfa) may be administered in addition to rVWF (vonicog alfa) in order to raise FVIII:C levels to recommended levels.

The detailed dosing calculations are provided in the protocol, as a general guidance, a loading dose of 40 to 60 IU/kg rVWF:RCo should be administered. ADVATE, at a dose of 30 to 45 IU/kg may be infused sequentially, preferably within 10 minutes after the rVWF infusion in subjects whose FVIII plasma levels already are (or are highly likely to be) less than 40 to 50 IU/dL for minor/oral surgery or 80 to 100 IU/dL for major surgery before the initiation of the surgery. At the discretion of the investigator, the ADVATE dose may be increased in subjects requiring emergency surgery who did not receive a preoperative priming dose.

The peri- and postoperative substitution regimen will be individualized according to PK results; intensity, and duration of the hemostatic challenge; and the institution's standard of care. Dosing should be guided by the dosing recommendations (provided in protocol) and continued until healing is achieved.

PK Assessment

For subjects in Cohort 4, the PK dose is 50 (±5) IU/kg rVWF:RCo for the initial PK assessment at the beginning of the study. Additionally, subjects in Cohorts 1-4 will undergo steady state PK assessment at the EOS, and the PK dose is their last scheduled prophylactic dose.

Methodology:

This is a Phase 3b, prospective, open-label, uncontrolled, non-randomized, multicenter study evaluating long-term safety and efficacy of rVWF (vonicog alfa) for prophylaxis (preventative treatment before bleeds occur) and OD (treatment of acute bleeds when they occur) treatment of bleeding episodes in pediatric and adult subjects with severe VWD. The study plans to include cohorts as below:

Prophylactic treatment cohorts

1. Adult subjects transitioning from the phase 3 Prophylaxis study (Study 071301) who will remain on the same prophylactic dose as in Study 071301
2. Adult subjects transitioning from Study 071301 with no clinically significant bleeding episode for the past 6 months who will start this phase 3b study at a lower dose/frequency compared to the dose received in Study 071301
3. Pediatric/adolescent subjects aged 12 to <18 years transitioning from the phase 3 pediatric study (Study 071102) who switch from receiving OD treatment to receiving once weekly or twice weekly prophylaxis
4. Newly enrolled adult and pediatric/adolescent (aged 12 to <18 years) subjects switching from OD treatment with VWF products, starting once weekly prophylaxis with rVWF (vonicog alfa) in this phase 3b extension study

On-demand treatment cohorts

5. Pediatric subjects of all ages from Study 071102 who will continue with receiving OD treatment
6. Adult subjects from Study 071301 who will switch back from prophylactic treatment to OD treatment

Adult subjects transitioning from Study 071301 who agree to continue prophylactic treatment will be given an opportunity to re-evaluate their prophylactic dose at the beginning of this study; if a subject experienced no bleeding episode over the last 6 months of their prophylactic treatment in Study 071301, the subject may be given a reduced dosage in this study (at the discretion of the principal investigator based on the detailed guidance provided in the protocol) (Cohort 2). Otherwise subjects will continue with the prophylactic treatment regimen from Study 071301 (Cohort 1), which is expected to be 50 (±10) IU/kg rVWF:RCo twice weekly for the majority of subjects.

Pediatric/adolescent subjects aged 12 to <18 years transitioning from the pediatric study 071102 who are considered eligible by the investigator for switching to prophylaxis may select to go on prophylactic treatment with rVWF (vonicog alfa) (Cohort 3) at a dose of either 50 (±10) IU/kg rVWF:RCo once weekly or twice weekly based on the investigator's assessment and recommendation. Dosage may be individualized within this range and, in consultation with the sponsor, increased up to 80 IU/kg if considered necessary to assure effective prophylaxis, based on: a) subject's available historical PK data; b) type and severity of bleeding episodes the subject has experienced; c) monitoring of appropriate clinical and laboratory measures for the subject.

Newly enrolled adult and pediatric/adolescent (aged 12 to <18 years) subjects (Cohort 4) will all be initially assigned to a prophylactic regimen of 50 (±10) IU/kg rVWF:RCo once per week with rVWF (vonicog alfa) if they are considered eligible and recommended by the investigator to receive prophylactic regimen and they choose to agree with the investigator's recommendation. The starting dose, after consultation with the Sponsor, can be increased up to 80 IU/kg if considered necessary to assure effective prophylaxis.

The remaining pediatric subjects (aged <18 years) from all age cohorts in Study 071102 who will not transition to prophylaxis (Cohort 5) and adult subjects from 071301 who are assigned (either based on medical assessment or individual preference) to switch back to OD regimen (Cohort 6) will receive rVWF (vonicog alfa) as OD (to treat acute bleeds when they occur) treatment in this study.

For all subjects on prophylactic treatment (Cohorts 1 to 4), dose and/or dose frequency will be increased based on bleeding episode dose-escalation criteria. (Please refer to Section 6.2.2.1.2 in the protocol for dose escalation details.)

For all cohorts, during the entire study observation period, any bleeding episodes requiring substitution therapy with VWF will be treated with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa). If surgery is needed, subjects will receive rVWF (vonicog alfa), with or without ADVATE (rFVIII, octocog alfa), for management of perioperative bleeding.

Once assigned, the cohort number of a subject will remain unchanged during the study. Change of treatment regimen will not result in switching of cohorts.

Minimum observation time for this study is 12 months and after this initial 12-month period, subjects will continue to be enrolled until rVWF (vonicog alfa) is commercially available in their respective countries or until subjects have been treated in the study for a maximum of 3 years, whichever occurs first.

Inclusion and Exclusion Criteria:

Inclusion Criteria:

Subjects who have completed Study 071301 or 071102 (or subjects who have completed the surgery arm treatment in Study 071102 and want to continue to receive OD treatment with rVWF) and are willing to immediately transition into this study, must meet the following 2 criteria to be eligible for this study:

1. If female of childbearing potential, has a negative blood/urine pregnancy test at screening and agrees to employ highly effective birth control measures (including sterilization, implant, intra-uterine device (IUD), correct and consistent use of hormonal contraception, and abstinence) for the duration of the study.
2. Subject and/or legally authorized representative is willing and able to comply with the requirements of the protocol.

New subjects (Cohort 4) who meet the above 2 and **ALL** the following additional criteria are eligible for this study:

3. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of substitution therapy with VWF concentrate required 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 (von Willebrand factor antigen [VWF:Ag] ≤3 IU/dL).

   Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.
4. Subject has been receiving OD therapy with VWF products for at least 12 months, and prophylactic treatment is recommended by the investigator.
5. Subject has ≥3 documented spontaneous bleeds (not including menorrhagia) requiring VWF treatment during the past 12 months.
6. Subject has available records that reliably evaluate type, frequency, and treatment of bleeding episodes for at least 12 months preceding enrollment; up to 24 months of retrospective data should be collected if available.
7. Subject is ≥12 years old at the time of screening and has a body mass index ≥15 but <40 kg/m^2.

Exclusion Criteria:

The subject will be excluded from the study if any of the following exclusion criteria are met:

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/international normalized ratio >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 Bethesda units (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 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 human immunodeficiency virus (HIV) positive with an absolute Helper T cell (CD4) count $<200/mm^3$.
8. 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, but not limited to 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) or liver cirrhosis classified as Child-Pugh class B or C.
9. The subject has been diagnosed with renal disease, with a serum creatinine (CR) level ≥2.5 mg/dL.
10. The subject has a platelet count <100,000/mL at screening (for subjects with type 2B VWD, platelet count(s) at screening will be evaluated taking into consideration historical trends in platelet counts and the Investigator's medical assessment of the patient's condition).
11. 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 (or assent, if appropriate).
12. The subject is pregnant or lactating at the time of enrollment.
13. The subject has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
14. 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.
15. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
16. For new OD subjects, the subject is scheduled for a surgical intervention.
17. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
18. 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.
19. 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 for screening

Only for Cohort 4, if the subject presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, and non-seasonal asthma) the screening visit will be postponed until the subject has recovered. For all other subjects, end-of-study (EOS) visit for 071102 or 071301 will be completed per protocol and the completed EOS visit in Study 071102 or 071301 will also serve as the screening visit for this continuation study (SHP677-304).

Maximum duration of subject participation in the study:

The planned duration of subject's participation is at least 12 months and up to maximum 3 years. The study will be completed in approximately 7 years.

Endpoints:

Primary Endpoint:

Efficacy of Prophylaxis
Spontaneous ABR during prophylaxis treatment with rVWF (vonicog alfa) based on the data collected during the first 12 months on study treatment.

Secondary Endpoints:

Safety:

- AEs/serious adverse events (SAEs): incidence, severity, causality
- Occurrence of thromboembolic events
- Occurrence of hypersensitivity reactions
- Immunogenicity
  a. Development of neutralizing antibodies (inhibitors) to VWF and FVIII
  b. Development of total binding antibodies to VWF and FVIII
  c. 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

Efficacy of Prophylaxis:

- Spontaneous ABR under prophylactic treatment with rVWF (vonicog alfa) while enrolled in the study
- Categorized weekly number of infusions defined as 1, 2 or ≥ 3 during prophylactic treatment with rVWF (vonicog alfa)
- Categorized spontaneous ABR defined as 0, 1-2, 3-5, or >5 bleeding episodes during rVWF (vonicog alfa) prophylaxis
- Time to first bleeding event under each prophylaxis regimen
- Spontaneous ABR by location of bleeding (Gastrointestinal [GI], epistaxis, joint bleeding, menorrhagia, oral, muscle and soft tissue, etc.) while on 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
- Transfusion free maintenance of hemoglobin and ferritin levels over time

Efficacy of the Treatment of Bleeding Episodes:

- Overall hemostatic efficacy rating at the resolution of bleed with respect to the treatment of bleeding episodes for the initial 12 months on study treatment
- Number of infusions of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) utilized to treat bleeding episodes while enrolled in the study
- Weight-adjusted consumption of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) per bleeding episode while enrolled in the study

Exploratory Endpoints:

Efficacy of Perioperative Management, if Surgery is Needed:
For the first 12 months on study treatment (except for the weight-adjusted dose, which is followed for the entire study period):

- 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
- Overall assessment of hemostatic efficacy by the Investigator 24 hours after the last perioperative infusion of rVWF (vonicog alfa) or at day 14 post-operation, whichever occurs first
- Daily intra- and postoperative weight-adjusted dose of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) through postoperative day 14

Pharmacokinetic Endpoints:

Pharmacokinetics (PK) and Pharmacodynamics (PD):

- PK parameters including initial assessment for Cohort 4 and EOS steady-state assessment for Cohorts 1 to 4: incremental recovery (IR), terminal half-life ($T_{½}$), 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 96 hours (AUC_{0-96h}), 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, VWF:Ag, von Willebrand factor collagen binding activity (VWF:CB). The corresponding PD of rVWF (vonicog alfa) as measured in FVIII activity (FVIII:C), based on the PK assessment will be assessed using C_{max}, T_{max}, and AUC_{0-96h}
- IR over time for the first 12 months of prophylaxis for all subjects in prophylactic Cohorts 1, 2, 3, and 4 at the scheduled follow-up visits

Health Economics and Outcomes Research Endpoints:

At baseline, 6 and 12 months, and EOS visit:

- HRQoL as assessed using Questionnaires:
  a. for adults (≥18 years of age):
     EuroQoL five-dimension questionnaire 3 level (EQ-5D-3L)
     Short Form (36) Health Survey (SF-36)
     Von Willebrand Impact Questionnaire (V-WIQ)
  b. for pediatric subjects aged 2 to <18 years at Screening:
     Pediatric Quality of Life Inventory™ (PedsQL™), and parent proxy versions:
     - PedsQL™ Teen report (ages 13 to 17) (23 items)
     - PedsQL™ Child report for children (ages 8 to 12) (23 items)
     - PedsQL™ Parent report for young children (ages 5 to 7) (23 items)
     - PedsQL™ Parent report for toddlers (ages 2 to 4) (21 items)

     EQ-5D-Y for subjects ≥7 years (parent-proxy version for ages 4 to <7 years)
     Pain: Visual analog scale (VAS)

- The nine-item Treatment Satisfaction Questionnaire for Medication (TSQM-9) (baseline assessment is not applicable for Cohort 4 newly enrolled subjects)
- Health resource utilization and productivity data, including number and duration of hospitalizations, emergency room visits, urgent care physician visits and days missed from school or work.

Statistical Analysis:

Analysis Sets

The safety analysis set will be composed of all subjects who received any amount of rVWF (vonicog alfa).

The full analysis set (FAS) will be composed of all enrolled subjects who received IP treatment.

The PK analysis set (PKAS) will be composed of all subjects who received at least one study drug infusion with one quantifiable post-dose measurement without any significant protocol deviations or events with potential to affect PK.

The per protocol analysis set (PPAS) will be composed of all subjects in the FAS who have no major deviations from the protocol affecting the study results with respect to efficacy. Major protocol deviations will be defined in the Protocol Deviation Plan.

Analysis of Primary Endpoint

The primary efficacy endpoint, spontaneous ABR during the first 12 months on prophylactic treatment with rVWF (vonicog alpha), will be calculated as the number of spontaneous (as assessed by the investigator) bleeds requiring treatment with a VWF product during the first 12 months on study treatment, and summarized through descriptive statistics by prophylactic cohort (Cohorts 1 to 4), and age group. The primary analysis will be based on the FAS and will be repeated on the PPAS as sensitivity analysis.

Analysis of Secondary Endpoints

Safety

Safety analysis will be performed on the safety analysis set by age group overall and by cohort, by dose regimen, if necessary, on 12, 24-month data and the entire study data.

Treatment-emergent AEs (TEAEs) are defined as AEs with start dates on or after the first exposure to IP. Summaries on AEs will be based on TEAEs unless otherwise indicated.

Frequency counts and percentages will be calculated for AEs and SAEs and presented in summary tables. AEs will be cross-tabulated for relatedness, seriousness, and severity. AEs will be categorized according to MedDRA dictionary and summarized by system organ class (SOC) and preferred term. Counts, frequency and annualized rates for thrombotic events and hypersensitivity reactions together with exact Clopper-Pearson 2-sided 95% confidence intervals (95% CI) on their occurrence will be tabulated.

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. Causally related AEs 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.

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 Chinese hamster ovary proteins, mouse IgG and rFurin.

Vital signs and laboratory parameters will be summarized descriptively. Shift tables will be prepared for laboratory parameters. Clinically significant abnormal values in routine laboratory parameters and vital signs will be summarized.

Efficacy of Prophylaxis

All secondary efficacy endpoints will be analyzed on the FAS by age group and cohort on 12-month data and the entire study. Continuous endpoints will be summarized by mean (2-sided 95% CI when appropriate), standard deviation (SD), median, range, and quartiles. Categorical endpoints will be summarized by proportions and 2-sided 95% CI will be provided when appropriate.

The spontaneous ABR (as calculated for the primary endpoint) will be summarized through descriptive statistics by prophylactic cohort (Cohorts 1 to 4) and age group.

For the cohorts receiving prophylactic treatment (cohorts 1 to 4) the number and proportion of subjects with dosing frequency of 1, 2, and ≥3 weekly will be evaluated at the end of 12-month treatment period and at the end of the study, in total and by cohort and age group, accompanied by a 2-sided 95% CI.

The number and proportion of subjects with categorized spontaneous ABR (i.e., 0, 1 to 2, 3 to 5, or >5 bleeds) will be provided by cohort and age group, accompanied by a 2-sided 95% CI.

Summary statistics for the time to first bleeding event under each prophylaxis treatment regimen will be provided by cohort and age group using Kaplan-Meier plots.

The spontaneous ABR (as calculated for the primary endpoint) will also be summarized by location of bleeding (GI, epistaxis, joint bleeding, menorrhagia, oral and other mucosa, muscle, and soft tissue, etc.).

Summary statistics for the total number of infusions, average number of infusions per week, as well as number (proportion) of subjects on different prophylaxis dosing regimens will be provided by cohort and age group when applicable and overall for prophylaxis arms. The total weight-adjusted consumption of rVWF (vonicog alfa) (and of ADVATE [rFVIII, octocog alfa] if applicable) during prophylactic treatment will be provided similarly.

The count and proportion of subjects that require no transfusion over time to maintain hemoglobin level will be calculated and summarized by cohort and age group. The ferritin levels over time will be summarized descriptively.

Efficacy of Treatment of Bleeding Episodes

The analysis will be performed on the FAS overall by age group and by treatment arm. The efficacy rating will be followed for the first 12 months (on study treatment) only.

For the number of infusions of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) per bleeding episode, for the weight-adjusted consumption of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) per bleeding event as well as for the overall hemostatic efficacy rating at resolution of bleed, summary statistics will be presented.

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

Analysis of Exploratory Outcome Measures:

Efficacy of Perioperative Management

The analysis will be performed on the FAS for the first 12 months of study data, except for the weight-adjusted dose that will be followed for the entire study.

Descriptive statistics will be performed for the following outcome measures:

- Intraoperative actual versus predicted blood loss (assessed by operating surgeon) at completion of surgery.
- Intraoperative hemostatic efficacy score on a scale of excellent, good, moderate or none (assessed by operating surgeon) at completion of surgery.
- Overall hemostatic efficacy by the investigator 24 hours after the last perioperative infusion of rVWF (vonicog alfa) or at day 14 post operation, whichever occurs first.
- Daily intra- and postoperative weight-adjusted dose of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) through postoperative day 14.

Pharmacokinetics and Pharmacodynamics

For subjects in the PKAS, the following PK parameters, based on the serial PK assessment, will be calculated for each adult subject and for each pediatric subject when applicable in Cohort 1, 2, 3, or 4 and reported using descriptive statistics for VWF:RCo, VWF:Ag and VWF:CB: IR, $T_{1/2}$, MRT, $AUC_{0-\infty}$, AUC_{0-96h}, C_{max}, T_{max}, V_{ss}, and CL. The corresponding PD of rVWF (vonicog alfa), as measured in FVIII activity (FVIII:C) based on the PK assessment, will be assessed using C_{max}, T_{max} and AUC_{0-96h}. These PD parameters will be listed and summarized descriptively.

Incremental recovery will be summarized by visit and displayed graphically over time for each subject in prophylactic cohorts (Cohort 1 to 4) for the initial 12 months of prophylactic treatment.

HRQoL, Treatment Satisfaction and Health Resource Utilization

The analysis will be performed on the FAS by cohort and age group at baseline, 6 and 12 months, and at the end of the study.

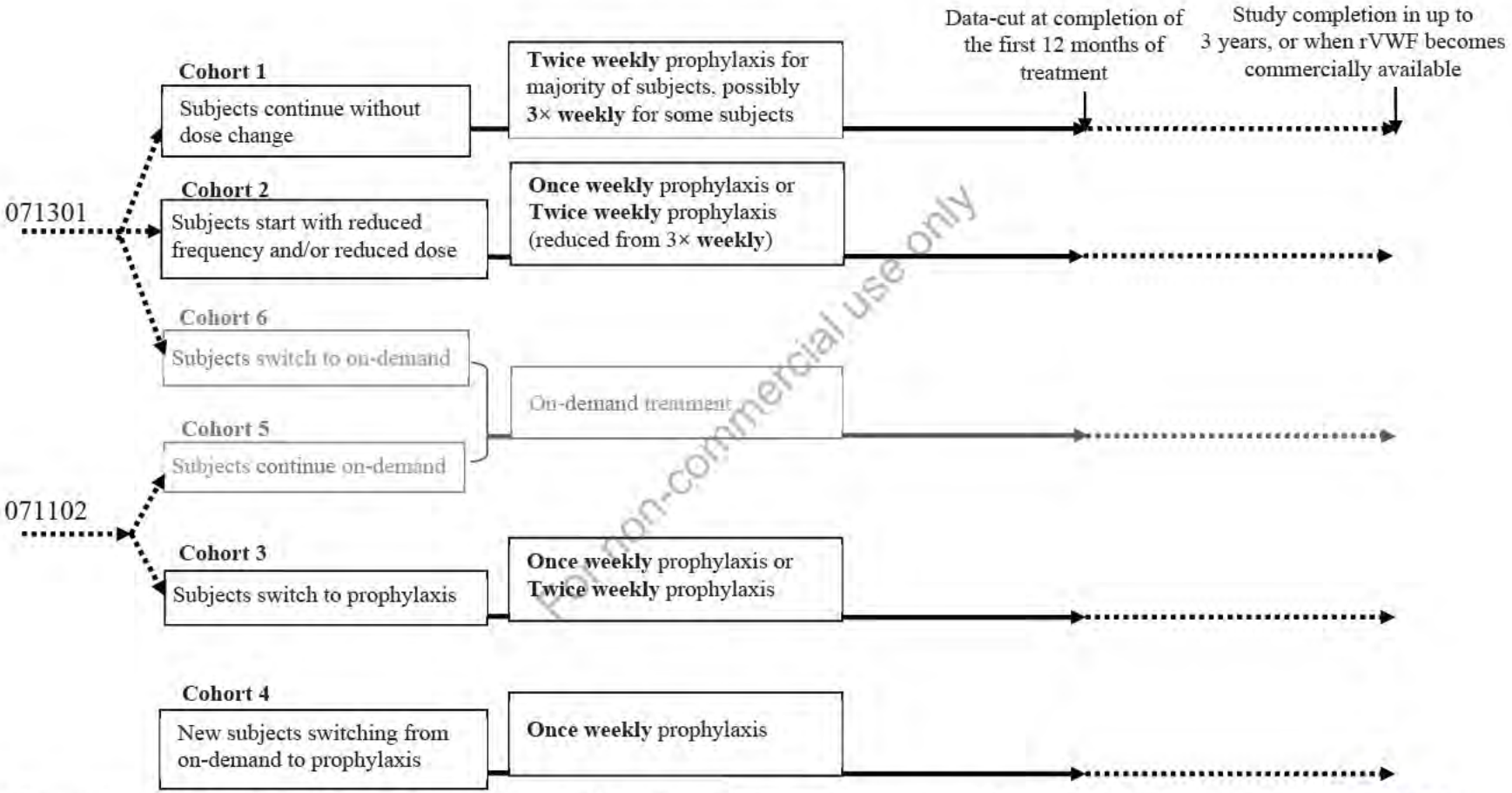
HRQoL, treatment satisfaction and health resource use data will be summarized descriptively and listed per subject. For all calculated scores of each questionnaire, descriptive statistics will be calculated by visit by age group and by cohort.

Interim Analysis

An interim analysis will be performed after all subjects in prophylactic treatment cohorts have completed their 12 months on study treatment. Additional interim analyses may be performed as needed to support submissions to health authorities.

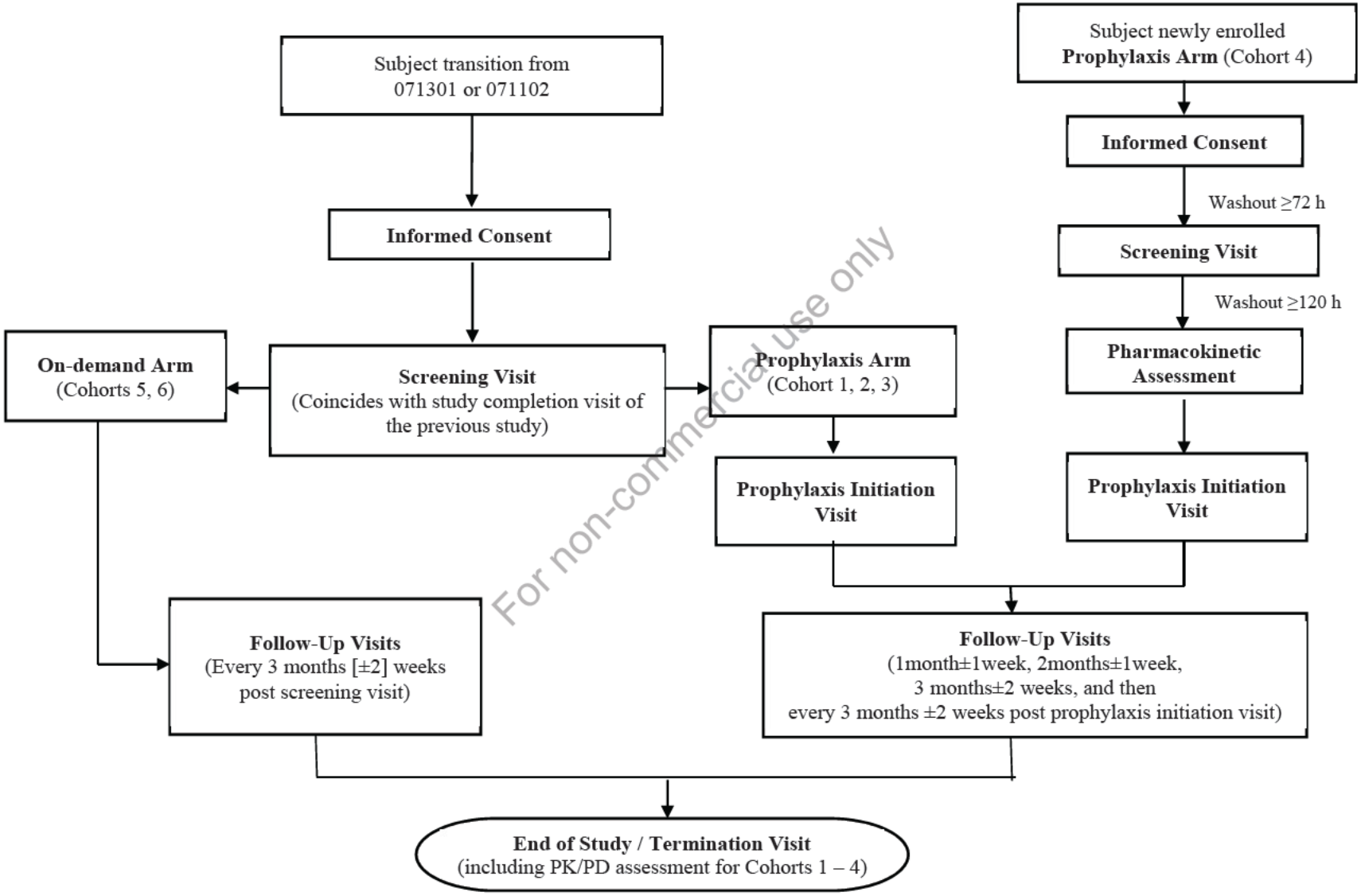
1.2 Schema

Figure 1. Study Schematic Diagram



For prophylaxis cohorts (Cohorts 1 to 4), dose escalation will be performed if escalation criteria are met during the study (see protocol Section 6.2.2.1.2 for details).
For all cohorts, subjects will receive rVWF (with or without ADVATE) for control of bleeding episodes and management of perioperative bleeding any bleeding episodes if needed.

Figure 2. Study Flow Chart



1.3 Schedule of Activities

Table 1. Schedule of Study Procedures and Assessments for On-demand Subjects Transitioning from Study 071301 or Study 071102 (Cohorts 5 and 6)

Procedures/Assessments	Screening Visit [a]	Follow-Up Study Visits					End of Study Visit
		3 months (±2) weeks	6 months (±2) weeks	9 months (±2) weeks	12 months (±2) weeks	Every 3 months (±2) weeks	
Informed Consent [b]	X						
Eligibility Criteria	X						
Medical History	*						
Physical Exam	*	X	X	X	X	X	X
Vital Signs [c]	*	X	X	X	X	X	X
Concomitant Medications and Non-drug Therapies [d]	*	X	X	X	X	X	X
Adverse Events [d]	*	X	X	X	X	X	X
Bleeding Episodes and On-demand Treatment [d]	*	X	X	X	X	X	X
Investigator Assessment of Hemostatic Efficacy [d]	*	X	X	X	X	X	X
Laboratories (See Table 5)	*	X	X	X	X	X	X
ECG	*		X		X		X
Subject Diary [e]	X	X	X	X	X	X	X
PROs (HRQoL, TSQM-9, etc.)	X		X		X		X

Table 1. Schedule of Study Procedures and Assessments for On-demand Subjects Transitioning from Study 071301 or Study 071102 (Cohorts 5 and 6)

Procedures/Assessments	Screening Visit [a]	Follow-Up Study Visits					End of Study Visit
		3 months (±2) weeks	6 months (±2) weeks	9 months (±2) weeks	12 months (±2) weeks	Every 3 months (±2) weeks	

ECG = electrocardiogram; HRQoL = health-related quality of life; IP = investigational product; PRO = patient-reported outcome; rVWF = recombinant von Willebrand factor; TSQM-9 = the nine-item Treatment Satisfaction Questionnaire for Medication

a. When possible, the screening visit should coincide with the end of study visit of the previous rVWF study (Study 071301 or Study 071102). The procedures/assessments marked with an asterisk (*) will be transcribed from the end of study visit of the previous rVWF study. If the following assessments are not part of the end of study assessments of the previous study, they must be performed at screening for this study (Study SHP677-304) to ensure subject's eligibility: viral serology, urinalysis, pregnancy test (if female of childbearing potential).

b. Occurs at enrollment (before screening). To give the subject sufficient time to review the informed consent form and to be aware of the treatment regimen prior to roll-over, this document should preferably be discussed with the subject and signed (if the subject agrees to continue in the Continuation study) prior to the end of study visit of the previous study.

c. Vital signs: weight, height, body temperature, pulse rate, respiratory rate, and blood pressure. Height is only required at the screening visit. If infusion of IP occurs on a 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.

d. Concomitant medications, non-drug therapies, adverse events, and bleeding episodes and their treatment will be continuously reviewed and specifically assessed at these times by the study sites and discussed with the subject.

e. E-diaries will be given out at screening and will be used to document all IP infusions including those for regular prophylaxis (study treatment), bleeds, treatment administered and response to IP, untoward events, concomitant medications and health resource use data. E-diaries are reviewed and discussed with the subject at each study visit. E-diary use is not optional; it is required per protocol. Therefore, if the subject or caregiver experiences any problem with the use of the e-diary, they should inform the site/Investigator immediately and follow the instructions given to record any information on the use of IP, including those for regular prophylaxis (study treatment) and to treat any acute bleed, on the bleeds experienced, untoward events, concomitant medications, and health resource use, until these data can be recorded in a properly working e-diary.

Table 2. Schedule of Study Procedures and Assessments for Prophylaxis Subjects Transitioning from Study 071301 or Study 071102 (Cohorts 1, 2, 3)

Procedures/ Assessments	Screening Visit [a]	Prophylaxis Initiation Visit [a]	Follow-Up Study Visits							End of Study Visit
			1 month (±1) week	2 months (±1) week	3 months (±2) weeks	6 months (±2) weeks	9 months (±2) weeks	12 months (±2) weeks	Every 3 months (±2) weeks	
Informed Consent [b]	X									See Table 9
Eligibility Criteria	X									
Medical History	*									
Physical Exam	*	X	X	X	X	X	X	X	X	
Vital Signs [c]	*	X	X	X	X	X	X	X	X	
IP Treatment [d]		X	X	X	X	X	X	X	X	
Concomitant Medications and Nondrug Therapies [e]	*	X	X	X	X	X	X	X	X	
Adverse Events [e]	*	X	X	X	X	X	X	X	X	
Bleeding Episodes and Treatment [e]	*	X	X	X	X	X	X	X	X	
Investigator Assessment of Hemostatic Efficacy [e]	*	X	X	X	X	X	X	X		
IR Determination [d]		X	X	X	X	X	X	X		
Laboratories (See Table 6)	*	X	X	X	X	X	X	X	X	
ECG	*					X		X		
Subject Diary [f]	X	X	X	X	X	X	X	X	X	
PROs (HRQoL, TSQM-9 etc.)		X				X		X		

Table 2. Schedule of Study Procedures and Assessments for Prophylaxis Subjects Transitioning from Study 071301 or Study 071102 (Cohorts 1, 2, 3)

ECG = electrocardiogram; HRQoL = health-related quality of life; IP = investigational product; IR = incremental recovery; PRO = patient-reported outcome; rVWF = recombinant von Willebrand factor; TSQM-9 = the nine-item Treatment Satisfaction Questionnaire for Medication

a. When possible, the screening visit should coincide with the end of study visit of the previous rVWF study (Study 071301 or Study 071102). The procedures/assessments marked with an asterisk (*) will be transcribed from the end of study visit of the previous rVWF study. If the following assessments are not a part of the end of study assessments of the previous study, they must be performed at screening to ensure subject's eligibility: viral serology, urinalysis, pregnancy test (if female of childbearing potential). The Prophylaxis Initiation Visit does not need to be a separate visit; it may occur on the same day as the screening visit in this study because the first prophylactic infusion of IP is expected to be administered on the day of the screening visit for all roll-over subjects from studies 071301 and 071102. Assessments should not be repeated if they are already performed/available at screening.

b. Occurs at enrollment (before screening). To give the subject sufficient time to review the informed consent form and to be aware of the treatment regimen prior to roll-over, this document should preferably be discussed with the subject and signed (if the subject agrees to continue in the Continuation study) prior to the end of study visit of the previous study.

c. Vital signs: weight, height, 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.

d. Investigational Product treatment after the prophylactic treatment initiation visit at the site will be continued as home-treatment if the subject or caregiver qualifies per criteria included in this protocol; 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 immunogenicity testing and IR determination is drawn.

e. Concomitant medications, non-drug therapies, adverse events, and bleeding episodes and their treatment will be continuously reviewed and specifically assessed at these times by the study sites and discussed with the subject.

f. E-diaries will be given out at screening and will be used to document all IP infusions including those for regular prophylaxis (study treatment), bleeds, treatment administered and response to investigational product (IP), untoward events, concomitant medications, and health resource use data. E-diaries are reviewed and discussed with the subject at each study visit. E-diary use is not optional; it is required per protocol. Therefore, if the subject or caregiver experiences any problem with the use of the e-diary, they should inform the site/Investigator immediately and follow the instructions given to record any information on the use of IP, including those for regular prophylaxis (study treatment) and to treat any acute bleed, on the bleeds experienced, untoward events, concomitant medications, and health resource use, until these data can be recorded in a properly working e-diary.

Table 3. Schedule of Study Procedures and Assessments for Newly Enrolled Subjects (Cohort 4)

Procedures/ Assessments	Screening Visit	PK Assessment [h]			Prophylaxis Initiation Visit [i]	Follow-Up Study Visits							End of Study Visit
		Pre-infusion [g]	Infusion	Post-infusion [g]		1 month (±1) week	2 months (±1) week	3 months (±2) weeks	6 months (±2) weeks	9 months (±2) weeks	12 months (±2) weeks	Every 3 months (±2) weeks	
Informed Consent [a]	X												See Table 10
Eligibility Criteria	X												
Medical History [b]	X												
Physical Exam	X	X			X	X	X	X	X	X	X	X	
Vital Signs [c]	X	X		X	X	X	X	X	X	X	X	X	
IP Treatment [d]			X		X	X	X	X	X	X	X	X	
Concomitant Medications and Non-drug Therapies [e]	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events [e]		X	X	X	X	X	X	X	X	X	X	X	
Bleeding Episodes and Treatment [e]	X	X	X	X	X	X	X	X	X	X	X	X	
Investigator Assessment of Hemostatic Efficacy [e]	X	X	X	X	X	X	X	X	X	X	X		
Laboratories (See Table 7)	X	X		X		X	X	X	X	X	X	X	
IR Determination					X	X	X	X	X	X	X		
ECG	X								X		X		
Subject Diary [f]	X				X	X	X	X	X	X	X	X	
PROs (HRQoL, TSQM-9, etc.)					X [j]				X		X		

Table 3. Schedule of Study Procedures and Assessments for Newly Enrolled Subjects (Cohort 4)

ECG=electrocardiogram; HRQoL=health-related quality of life; IP=investigational product; IR=incremental recovery; PK=pharmacokinetic; PRO=patient-reported outcome; rVWF = recombinant von Willebrand factor; TSQM-9= the nine-item Treatment Satisfaction Questionnaire for Medication

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. 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.
d. Investigational product 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 immunogenicity testing and IR determination is drawn.
e. Concomitant medications, non-drug therapies, adverse events, and bleeding episodes and their treatment will be continuously reviewed and specifically assessed at these times by the study sites and discussed with the subject.
f. E-diaries will be given out at screening and will be used to document all IP infusions including those for regular prophylaxis (study treatment), bleeds, treatment administered and response to IP, untoward events, concomitant medications, and health resource use data. E-diaries are reviewed and discussed with the subject at each study visit. E-diary use is not optional; it is required per protocol. Therefore, if the subject or caregiver experiences any problem with the use of the e-diary, they should inform the site/Investigator immediately and follow the instructions given to record any information on the use of IP, including those for regular prophylaxis (study treatment) and to treat any acute bleed, on the bleeds experienced, untoward events, concomitant medications, and health resource use, until these data can be recorded in a properly working e-diary.
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 (can be performed at 10 (±1) hours for the subject's convenience), 24 (±0.5) hours, 30 (±2) hours, 48 (±2) hours, 72 (±2) hours and 96 (±2) hours.
h. Pharmacokinetic assessments to be performed following a washout period of at least 5 days. The subject should not be actively bleeding at the time of PK assessment.
i. 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). The 96 h post-infusion PK sampling should be conducted on the same day along with the drawing of prophylaxis pre-infusion sample.
j. Baseline assessment of TSQM-9 at prophylaxis initiation visit is not applicable for Cohort 4 newly enrolled subjects.

Table 4. Schedule of 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 (post-operative Day 1 → end of perioperative IP treatment) [a]		
ECG						X
Physical examination	X	X		X	X	X
Adverse events	X	X	X	X	X	X
Laboratories (See Table 8)	X	X	X	X	X	X
Vital signs [b]	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
Hemostatic efficacy assessments [c]			X	X	X	X
Blood loss		X estimated	X actual	X	X [d]	X [d]
Treatment days estimate		X				

ECG=electrocardiogram; IP=investigational product; HRQoL=health-related quality of life; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor

a. The assessments will be performed daily from Day 1 post the surgery day until perioperative IP treatment end (potentially multi-visits).
b. Vital signs: within 30 minutes before infusion start and 30 ± 15 minutes post-infusion.
c. Completed immediately post-surgery by the operating surgeon 24 hours post last IP infusion or at Day 14 visit (whichever occurs first) by the investigator.
d. In case bleeding still ongoing.

Table 5. Clinical Laboratory Assessments for On-demand Subjects (Cohorts 5 and 6)

Procedures/Assessments	Screening Visit [a]	Follow-Up Study Visits					End of Study Visit
		3 months (±2) weeks	6 months (±2) weeks	9 months (±2) weeks	12 months (±2) weeks	Every 3 months (±2) weeks	
Hematology [b]	*	X	X	X	X	X	X
Clinical Chemistry [c]	*	X	X	X	X	X	X
Coagulation Panel [d]	*	X	X	X	X	X	X
Immunogenicity [e]	*	X	X	X	X	X	X
Viral Serology [f]	*						
Urinalysis [g]	*						
VWD Gene Mutational Analysis and Analysis of VWF multimers [h]	*						
sP-selectin and D-dimer	X [i]						
Blood Group	*						
Pregnancy Test [j]	*						

a. When possible, the screening visit should coincide with the end of study visit of the previous recombinant von Willebrand factor (rVWF) study (Study 071301 or Study 071102). The procedures/assessments marked with an asterisk (*) will be transcribed from the end of study visit of the previous rVWF study if available.

b. 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), platelet count and serum Ferritin (Fe). For visits during which IP is administered on site, blood samples should be drawn within 60 minutes pre-infusion.

c. Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, bicarbonate, blood urea nitrogen (BUN), albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total protein, and bilirubin - direct and total. For visits during which IP is administered on site, blood samples should be drawn within 60 minutes pre-infusion.

d. Coagulation panel: prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (aPTT) (only for screening), von Willebrand factor: Ristocetin cofactor (VWF:RCo), von Willebrand Factor antigen (VWF:Ag), von Willebrand factor collagen binding activity (VWF:CB), factor VIII clotting activity (FVIII:C).

e. 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 (tested at screening and all subsequent study visits), Binding Ab to Chinese hamster ovary (CHO) protein, Binding Ab to rFurin, Binding Ab to Murine IgG (tested at screening, every 6 months during follow-up, and at the End of Study visit). In case of a serious

Table 5. Clinical Laboratory Assessments for On-demand Subjects (Cohorts 5 and 6)

Procedures/Assessments	Screening Visit [a]	Follow-Up Study Visits					End of Study Visit
		3 months (±2) weeks	6 months (±2) weeks	9 months (±2) weeks	12 months (±2) weeks	Every 3 months (±2) weeks	

adverse event (SAE) hypersensitivity reaction, IgE antibodies to VWF may 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.

f. Viral Serology: Hepatitis A Antibody, Total; Hepatitis A Antibody, IgM; Hepatitis B Surface Antibody; Hepatitis B Core Antibody, Total; Hepatitis B Core Antibody, IgM; Hepatitis B Surface Antigen; Hepatitis C Virus Antibody; Parvovirus B19; Human Immunodeficiency Virus (HIV-1/HIV-2) Antibodies

g. Urinalysis: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH

h. Not required if available in the subject's medical history; additionally, in case of a thromboembolic event, VWF multimers and A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, number 13 (ADAMTS13) will be analyzed to evaluate a possible causal relatedness to ultra-high molecular weight (UHMW) fractions of the IP.

i. At screening and in case of thromboembolic events

j. Serum pregnancy test (in females of child-bearing potential if no urine sample is available). Pregnancy test is scheduled at the screening and, if deemed necessary by principal investigator (PI), can be performed on an ongoing basis, at any time during the study.

Table 6. Clinical Laboratory Assessments for Prophylaxis Subjects Transitioning from Study 071301 or Study 071102 (Cohorts 1, 2, 3)

Procedures/ Assessments	Screening Visit [a]	Prophylaxis Initiation Visit [a]	Follow-Up Study Visits							End of Study Visit
			1 month (±1) week	2 months (±1) week	3 months (±2) weeks	6 months (±2) weeks	9 months (±2) weeks	12 months (±2) weeks	Every 3 months (±2) weeks	
Hematology [b]	*	X	X	X	X	X	X	X	X	See Table 9
Clinical Chemistry [c]	*	X	X	X	X	X	X	X	X	
Coagulation Panel [d]	*	X	X	X	X	X	X	X	X	
Immunogenicity [e]	*	X	X	X	X	X	X	X	X	
Viral Serology [f]	*									
Urinalysis [g]	*									
VWD Gene Mutational Analysis and Analysis of VWF multimers [h]	*									
sP-selectin and D-dimer	X [i]									
Blood Group	*									
Pregnancy Test [j]	*									

Table 6. Clinical Laboratory Assessments for Prophylaxis Subjects Transitioning from Study 071301 or Study 071102 (Cohorts 1, 2, 3)

a. When possible, the screening visit should coincide with the end of study visit of the previous recombinant von Willebrand factor (rVWF) study (Study 071301 or Study 071102). The procedures/assessments marked with an asterisk (*) will be transcribed from the end of study visit of the previous rVWF study if available. The Prophylaxis Initiation Visit does not need to be a separate visit; it may occur on the same day as the screening visit because the first prophylactic infusion of IP is expected to be administered on the day of the screening visit.

b. 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), platelet count and serum Ferritin (Fe). For IP-associated visits, samplings are within 60 minutes pre-infusion.

c. Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, bicarbonate, blood urea nitrogen (BUN), albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total protein, and bilirubin - direct and total. For IP-associated visits, samplings are within 60 minutes pre-infusion.

d. Coagulation panel (also refers to incremental recovery [IR] pre/post dose assessments at prophylaxis initiation visit and each follow-up visit): prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (aPTT) (only for screening), von Willebrand factor: Ristocetin cofactor (VWF:RCo), von Willebrand factor antigen (VWF:Ag), von Willebrand factor collagen binding activity (VWF:CB), factor VIII clotting activity (FVIII:C); for IR, samples will be drawn within 30 minutes pre-infusion and 30 ± 5 minutes post-infusion. After the 12-month visit, samples for coagulation testing need to be drawn only pre-infusion in order to process the immunogenicity testing.

e. 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 (tested at screening and all subsequent study visits), Binding Ab to Chinese hamster ovary (CHO) protein, Binding Ab to rFurin, and Binding Ab to Murine IgG (tested at screening, every 6 months during follow-up, and at the End of Study visit). In case of a serious adverse event (SAE) hypersensitivity reaction, IgE antibodies to VWF may 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.

f. Viral Serology: Hepatitis A Antibody, Total; Hepatitis A Antibody, IgM; Hepatitis B Surface Antibody; Hepatitis B Core Antibody, Total; Hepatitis B Core Antibody, IgM; Hepatitis B Surface Antigen; Hepatitis C Virus Antibody; Parvovirus B19; Human Immunodeficiency Virus (HIV-1/HIV-2) Antibodies.

g. Urinalysis: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH

h. Not required if available in the subject's medical history; additionally, in case of a thromboembolic event, VWF multimers and A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, number 13 (ADAMTS13) will be analyzed to evaluate a possible causal relatedness to ultra-high molecular weight (UHMW) fractions of the IP.

i. At screening and in case of thromboembolic events

j. Serum pregnancy test (in females of child-bearing potential if no urine sample is available). Pregnancy test is scheduled at the screening and, if deemed necessary by principal investigator (PI), can be performed on an ongoing basis, at any time during the study.

Table 7. Clinical Laboratory Assessments for Newly Enrolled Subjects (Cohort 4)

Procedures/ Assessments	Screening Visit	PK Assessment [a]			Prophylaxis Initiation Visit	Follow-Up Study Visits							End of Study Visit
		Pre-infusion	Infusion	Post-infusion		1 month (±1) week	2 months (±1) week	3 months (±2) weeks	6 months (±2) weeks	9 months (±2) weeks	12 months (±2) weeks	Every 3 months (±2) weeks	
Hematology [b]	X	X		X	X	X	X	X	X	X	X	X	See Table 10
Clinical Chemistry [c]	X	X		X	X	X	X	X	X	X	X	X	
Coagulation Panel [d]	X	X		X	X	X	X	X	X	X	X	X	
Immunogenicity [e]	X	X			X	X	X	X	X	X	X	X	
Viral Serology [f]	X												
Urinalysis [g]	X												
VWD Gene Mutational Analysis and Analysis of VWF multimers [h]	X												
sP-selectin and D-dimer	X [i]												
Blood Group	X												
Pregnancy Test [j]	X												

a. Pharmacokinetic assessments to be performed following a washout period of at least 5 days. The subject should not be actively bleeding at the time of pharmacokinetic (PK) assessment. 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 investigational product (IP) infusion for prophylactic treatment (prophylactic treatment initiation visit). The 96 h post-infusion PK sampling should be conducted on the same day along with the drawing of prophylaxis pre-infusion sample.

b. 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), platelet count and serum Ferritin (Fe). 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.

c. Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, bicarbonate, blood urea nitrogen (BUN), albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total protein, and bilirubin - direct and

Table 7. Clinical Laboratory Assessments for Newly Enrolled Subjects (Cohort 4)

total. 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.

d. Coagulation panel/PK assessment (also refers to IR pre/post dose assessments at prophy initiation visit and each follow-up visit until the 12-month visit): prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (aPTT) (only for screening), von Willebrand factor: Ristocetin cofactor (VWF:RCo), von Willebrand factor antigen (VWF:Ag), von Willebrand factor collagen binding activity (VWF:CB), factor VIII clotting activity (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 (can be made at 10(±1) hours for convenience), 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. After the 12-month visit, samples for coagulation testing need to be drawn only pre-infusion in order to process the immunogenicity testing.

e. 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 (tested at screening and all subsequent study visits), Binding Ab to Chinese hamster ovary (CHO) protein, Binding Ab to rFurin, and Binding Ab to Murine IgG (tested at screening, every 6 months during follow-up, and at the End of Study visit). In case of a serious adverse event (SAE) hypersensitivity reaction, IgE antibodies to VWF may 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.

f. Viral Serology: Hepatitis A Antibody, Total; Hepatitis A Antibody, IgM; Hepatitis B Surface Antibody; Hepatitis B Core Antibody, Total; Hepatitis B Core Antibody, IgM; Hepatitis B Surface Antigen; Hepatitis C Virus Antibody; Parvovirus B19; Human Immunodeficiency Virus (HIV-1/HIV-2) Antibodies

g. Urinalysis: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH

h. Not required if available in the subject's medical history; additionally, in case of a thromboembolic event, VWF multimers and A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, number 13 (ADAMTS13) will be analyzed to evaluate a possible causal relatedness to ultra-high molecular weight (UHMW) fractions of the IP.

i. At screening and in case of thromboembolic events

j. Serum pregnancy test (in females of child-bearing potential if no urine sample is available). Pregnancy test is scheduled at the screening and, if deemed necessary by principal investigator (PI), can be performed on an ongoing basis, at any time during the study.

Table 8. Laboratory Sampling for Surgical Bleeding

Procedures/ Assessments[a]	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 (post- operative 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						

Table 8. Laboratory Sampling for Surgical Bleeding

[a] Blood draws are within 3 hours 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 from Day 1 post the surgery day until perioperative investigational product (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), platelet count and serum Ferritin (Fe).

[d] Not required if sample already drawn at the time of the priming dose.

[e] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, bicarbonate, blood urea nitrogen (BUN), albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total protein, and bilirubin - direct and total.

[f] Coagulation panel: von Willebrand factor: Ristocetin cofactor (VWF:RCo), von Willebrand factor antigen (VWF:Ag), factor VIII clotting activity (FVIII:C) prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (aPTT); in addition to pre-infusion, 30 ± 5 minutes post infusion blood draw is needed.

[g] 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 (tested at screening and all subsequent study visits), Binding Ab to Chinese hamster ovary (CHO) protein, Binding Ab to rFurin, and Binding Ab to Murine IgG (tested at screening and the Post-operative Day 14 visit). In case of a serious adverse event (SAE) hypersensitivity reaction, IgE antibodies to VWF may be determined.

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

[i] VWD multimers and A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, number 13 (ADAMTS13) during the study only in case of thrombotic events

Table 9
End of Study Procedures and Assessments for Subjects in Cohorts 1, 2, 3, and 4

Procedures/ Assessments	PK Assessment at Study Completion			Termination Visit
	Pre-infusion[a]	Infusion	Post-infusion[a]	Conducted at the 96 hour postinfusion PK Assessment
Physical Examination	X		X	X
Vital Signs[b]	X		X	X
ECG				X
Concomitant Medications and Non-drug Therapies[c,d]	X	X	X	X
rVWF Treatment[e]		X		
PK Samples[a]	X		X	
Adverse Events[d]	X	X	X	X
Bleeding Episodes and Treatment[d]				X
Subject Diary[f]				X
PROs (HRQoL, TSQM-9, etc.)				X
Hematology[g]	X		X	X
Clinical Chemistry[h]	X		X	X
Coagulation Panel[i]	X		X	
Immunogenicity[j]	X			
Pregnancy Test[k]				

Table 9
End of Study Procedures and Assessments for Subjects in Cohorts 1, 2, 3, and 4

Procedures/ Assessments	PK Assessment at Study Completion			Termination Visit
	Pre-infusion[a]	Infusion	Post-infusion[a]	Conducted at the 96 hour postinfusion PK Assessment

[a.] 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.

[b.] Vital signs: weight, body temperature, pulse rate, respiratory rate, and blood pressure. 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.

[c] Including all concomitant medications and non-drug therapies taken during the course of the study.

[d] Concomitant medications, non-drug therapies, adverse events, and bleeding episodes and their treatment will be continuously reviewed and specifically assessed at these times by the study sites and discussed with the subject.

[e] A wash-out period of at least 72 hours is required after the last IP infusion before the PK assessment at study completion. IP infusion will be given at the study site after the blood sample for immunogenicity testing is drawn.

[f] E-diaries will be given out at screening and will be used to document all IP infusions including those for regular prophylaxis (study treatment), bleeds, treatment administered and response to investigational produce, untoward events, concomitant medications and health resource use data. E-diaries used throughout the study are reviewed and discussed with the subject at each study visit, and they will be reviewed with the subject and collected at the EOS visit.

[g.] 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), platelet count and serum Ferritin (Fe). For IP-associated visits, samplings are within 60 minutes pre-infusion.

[h.] Clinical chemistry assessments include: Sodium, potassium, chloride, glucose, creatinine, bicarbonate, blood urea nitrogen (BUN), albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total protein, and bilirubin - direct and total. For IP-associated visits, samplings are within 60 minutes pre-infusion.

[i.] Coagulation panel for PK assessment: von Willebrand factor: Ristocetin cofactor (VWF:RCo), von Willebrand factor antigen (VWF:Ag), von Willebrand factor collagen binding activity (VWF:CB), factor VIII clotting activity (FVIII:C).

[j.] Immunogenicity assessment includes Neutralizing Antibodies (Ab) to factor VIII (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 Chinese hamster ovary (CHO) protein, Binding Ab to rFurin, and Binding Ab to Murine IgG. In case of a serious adverse event (SAE) hypersensitivity reaction, IgE antibodies to VWF may be determined. A washout period of at least 72 hours after the last rVWF infusion is required before blood samples for immunogenicity assessments can be drawn.

[k.] Serum pregnancy test (in females of child-bearing potential if no urine sample is available). Pregnancy test is scheduled at the screening and, if deemed necessary by principal investigator (PI), can be performed on an ongoing basis, at any time during the study.

2. INTRODUCTION

2.1 Indication and Current Treatment Options

Von Willebrand disease (VWD) is the most frequently inherited bleeding disorder, affecting approximately 1% of the general population, although the incidence of clinically relevant cases is lower, about 100 cases per million (Gill 2007; Goodeve et al. 2010; Mannucci 2004).

VWD is classified into 3 main types (1, 2, and 3) with peculiar phenotype and genotype (Gill 2007):

1. Type 1 VWD, accounting for up to 70% of patients diagnosed with von Willebrand factor (VWF) disease, is a partial quantitative deficiency, induced by mutations, mostly missense mutations that produce a wide range of pathophysiologic effects including abnormal transcription, subcellular storage and secretion and accelerated clearance. Type 1 VWD patients mostly display mild clinical symptoms.
2. Type 2 VWD, which accounts for about 20% to 30% of the patients, is further divided into 4 subtypes (2A, 2B, 2M, and 2N), reflecting distinct classes of functional abnormalities. Mutations causing VWD types 2A, 2B, 2M, 2N variously affect VWF multimer assembly and proteolysis, VWF-dependent platelet adhesion, or the VWF factor VIII (FVIII) binding site. The bleeding diathesis is usually moderate and affects primarily the mucosal tissues. Patients with 2N VWD are sometimes misdiagnosed as having mild hemophilia A.
3. Type 3 VWD, account for 1% to 5% of VWD patients, exhibiting a total or near total absence of VWF protein and activity and consequently very low FVIII levels (<10 IU/dL) (Sadler et al. 2006). Type 3 VWD is associated with severe hemorrhagic symptoms (bleeding occurs in mucosal tissues, muscle, and joints). The inheritance pattern is codominant alleles (with both parents exhibiting type 1 VWD). The mutations responsible for type 3 VWD are highly varied and include large deletions in the VWF gene as well as missense mutations that prevent VWF biosynthesis and secretion.

All VWD patients, particularly those with type 2 or type 3 disease, are at increased risk for life-threatening bleeding, requiring immediate or even prophylactic VWF replacement therapy to correct VWF deficiency and/or the secondary FVIII deficiency. The aim of VWD treatment is to correct the dual defect of hemostasis, i.e., the abnormal coagulation expressed by low levels of FVIII and abnormal platelet adhesion expressed by the prolonged bleeding time. Desmopressin (1-deamino- 8-D-arginine-vasopressin, DDAVP) is the treatment of choice for type 1 VWD because it induces the release of normal VWF from cellular compartments that correct the FVIII/VWF levels and the prolonged bleeding time in the majority of cases (Castaman et al. 2003). In type 3 and severe forms of types 1 and 2 VWD, DDAVP is not

effective; therefore, for these patients, FVIII and VWF replacement therapy is used in bleedings, surgery, and secondary long-term prophylaxis (Mannucci 2004).

2.2 Product Background and Clinical Information

VWF is a large multimeric glycoprotein (with multimers ranging in molecular weight from 500 to >20000 kDa) that is normally found in plasma, alpha-granules of platelets, and intracellular organelles known as Weibel-Palade bodies. The VWF is carrier molecule for FVIII, an essential cofactor of secondary hemostasis that leads to fibrin clot formation, and facilitates platelet adhesion to subendothelium at sites of vascular injury (Hantgan et al. 1990).

Human VWF produced by recombinant technology provides a new perspective in treatment of VWD (Fischer 1999). Limitations associated with plasma-derived VWF (pdVWF) concentrates can be overcome by recombinant VWF (rVWF). Takeda (formerly Baxalta and later Shire; hereafter referred to as the sponsor) has developed an rVWF, which is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line that expresses the VWF gene (Turecek et al. 2010). The differences between pdVWF and rVWF are listed in Table 10.

Table 10. Differences Between Plasma-Derived and Recombinant von Willebrand Factor

Plasma-Derived VWF	Recombinant VWF
Synthesized in the endothelial cells and megakaryocytes	Expressed in CHO cells
Post-translational modification of propeptide removal occurs intracellularly during passage of the protein from the Golgi to the post-Golgi compartments	Pro-peptide removal is induced in vitro through exposure of the pro-VWF to a second recombinant protein (the propeptide processing enzyme Furin)
Consists of VWF subunits that have been exposed to ADAMTS13 (a multi-domain metalloprotease that cleaves the VWF subunits at the TYR1605 - MET1606 bond in the A2 domain), resulting in VWF subunits/multimers that have decreased hemostatic potential	Consists of intact VWF subunits including ultra-large VWF (UL-VWF) multimers as the rVWF has not been exposed to ADAMTS13
ABO-glycan structures are present	ABO-glycan structures are absent

ADAMTS13=A murine disintegrin and metalloproteinase with a thrombospondin type 1 motif, number 13; VWF=von Willebrand factor; CHO=Chinese hamster ovary

To address concerns that blood-borne pathogens may be associated with human plasma, the process does not employ any exogenously added raw materials of human or animal origin 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 G (IgG) (from the immunoaffinity purification of ADVATE and rVWF); host cell (i.e., CHO) protein; rFurin, a propeptide processing enzyme that is used to mature the pro-rVWF into active rVWF; and rFVIII. Consequently, the theoretical risk of contamination

with an adventitious virus is minimal. Recombinant VWF has undergone extensive in vitro and in vivo non-clinical investigation supporting its safe evaluation in humans. The clinical development program consists of 5 completed trials (4 in VWD and 1 in hemophilia). Available data support the safety and efficacy of rVWF (and rVWF administered with ADVATE for the first dose to correct FVIII deficiency) for the prevention and treatment of spontaneous and trauma-induced bleeding episodes in adults (18 to 64 years) diagnosed with VWD.

Recombinant VWF was granted licensure in the United States in December 2015 under the brand name VONVENDI for on-demand (OD) treatment and control of bleeding episodes in adults diagnosed with VWD, and has been available on the market since August 2016. Also, in April 2018, VONVENDI was approved by the Food and Drug Administration (FDA) in the United States (US) for the additional indication of perioperative management of bleeding in adults (age 18 and older) diagnosed with VWD. On 31 August 2018, the European Commission implemented the decision granting marketing authorization for VEYVONDI (vonicog alfa) for the treatment of hemorrhage 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. On 4 October 2018, VEYVONDI (vonicog alfa) was granted licensure in Switzerland by Swissmedic for the treatment of hemorrhage or surgical bleeding in VWD, when desmopressin (DDAVP) treatment alone is ineffective or contra-indicated. VEYVONDI should not be used in the treatment of Hemophilia 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. On 25 March 2020, VONVENDI was authorized in Japan by Ministry of Health, Labour and Welfare (MHLW) for treatment and control of bleeding tendency in patients diagnosed with VWD. On 15 April 2020, VEYVONDI was authorized in Australia by Therapeutic Goods Administration (TGA) for treatment of haemorrhage and surgical bleeding and for prevention of surgical bleeding in adults (age 18 and older) with VWD, when desmopressin (DDAVP) treatment alone is ineffective or not indicated.

A detailed description of rVWF is also provided in the investigator's brochure (IB).

2.2.1 Nonclinical Studies

2.2.1.1 Primary Pharmacodynamics

Primary pharmacodynamics (PD) were evaluated in different surrogate models of efficacy using VWF-deficient mice, VWF-deficient dogs, and VWF-deficient pigs. An in vitro PD study provided evidence that rVWF containing ultralarge multimers (ULM) is beneficial with respect to formation of rVWF-platelet conglomerates and that recombinant A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, number 13 (ADAMTS13) is an effective regulatory counterpart to ultralarge rVWF multimers.

2.2.1.2 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 (BP), cardiac, and respiratory functions 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.

2.2.1.3 Pharmacokinetics

Pharmacokinetic (PK) 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 plasma concentration/time 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 were not affected by co-administration of rVWF in cynomolgus monkeys. The PK data in the FVIII knock out 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.

2.2.1.4 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 ADAMTS13 does not decrease the ultra-large molecular weight multimers of rVWF (Varadi et al. 2009). 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 von Willebrand factor: Ristocetin cofactor (VWF:RCo)/kg/day + 1080 IU ADVATE/kg/day intravenously (IV) 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 (Varadi et al. 2009). No toxicologically relevant changes were evident for clinical observations, body weight (BW), 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 IV (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 IV 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 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 3 different hemophilic mouse models.

Please see Section 4 of the IB for further details on non-clinical studies of rVWF.

2.2.2 Clinical Studies

2.2.2.1 Completed Studies

To date, the clinical development program consists of 5 completed trials of rVWF in VWD:

1. Phase 1 Study 070701, which investigated PK and tolerability in patients with severe type 1, type 2, and type 3 VWD
2. Phase 3 Study 071001, which investigated the efficacy, safety, and PK of rVWF in patients with severe VWD
3. Phase 3 Study 071401, which included a single subject who was in urgent need of rVWF due to anaphylactic reactions to pdVWF
4. Phase 3 Study 071101, which investigated the safety and efficacy of rVWF in VWD patients undergoing elective surgical and invasive procedures.
5. Phase 3 Study 071301, investigating the efficacy and safety of prophylaxis with rVWF in adult subjects with severe VWD

In addition, a Phase 1 study (071104), which investigated the safety of rVWF administered together with recombinant FVIII (rFVIII; ADVATE) in hemophilia A patients has also been conducted.

The results of Phase 1 Study 070701 showed rVWF administered with rFVIII (ADVATE) at a ratio of 1.3:1 to be safe and well tolerated in adult patients with severe VWD up to the highest investigated dose of 50 IU/kg VWF:RCo. The results of the Phase 1 study supported further evaluation of rVWF. The completed Phase 3 Study 071001 investigated the efficacy and safety of rVWF for the treatment of bleeding episodes when administered with ADVATE for the first infusion, and without ADVATE for the subsequent infusions (if needed) as long as hemostatic FVIII clotting activity (FVIII:C) levels (>40%) were maintained. rVWF was shown to be safe and well tolerated. Most of the bleeds (81.8%) were controlled with 1 infusion of rVWF.

The PK profile for rVWF is comparable to plasma-derived VWF:FVIII (pdVWF:pdFVIII) concentrate with a tendency toward a longer VWF:RCo half-life ($T_{1/2}$) and sustained stabilization of FVIII:C, obviating the need for additional rFVIII after the first infusion. rVWF was well tolerated in Study 071104 in subjects with hemophilia A. A slight trend was observed towards a higher $T_{1/2}$ of rFVIII when administered together with 50 IU/kg rVWF, with the highest increase in rFVIII $T_{1/2}$ in subjects with the lowest VWF antigen (VWF:Ag) baseline levels.

Study 071101 evaluated the efficacy and safety of rVWF with or without ADVATE in subjects with severe VWD undergoing major, minor, or oral elective surgical procedures. The study showed rVWF to be safe and well tolerated. Intra- and postoperative hemostasis were rated "excellent" or "good" for all treated subjects. As expected, postinfusion increases in concentrations of VWF:RCo, VWF:Ac, VWF:Ag, von Willebrand factor collagen binding activity (VWF:CB), and FVIII:C were observed. The VWF:RCo activity was consistent with that previously observed in clinical studies (Study 071001 and Study 070701).

Study 071301 evaluated the efficacy and safety of prophylactic treatment with rVWF at a starting dose of 40 to 60 IU/kg twice weekly in subjects with severe VWD. The study showed rVWF to be safe and well tolerated. Prophylaxis with rVWF reduced the mean on-study spontaneous treated annualized bleeding rate (sABR) by 95% in subjects who switched from OD with a VWF to prophylactic treatment with rVWF (Prior OD subjects) and by 45% in subjects who switched from prophylaxis with plasma-derived VWF to rVWF prophylaxis (Switch subjects). Most (78.3%) subjects had zero treated spontaneous BEs while on rVWF prophylaxis. FVIII activity trough levels increased significantly for the Prior OD group from the initial assessment to the final assessment (geometric least squares [LS] means of 3.83 IU/dL and 18.7 IU/dL at the initial and final assessments, respectively; $p<0.0001$). For the Switch group, trough levels of FVIII activity from the first PK/PD assessment (done after 5 to 6 infusions of

rVWF) were similar to trough levels at study completion (both assessments done at steady state). Comparable dose-normalized C_{max} and AUC of FVIII activity at steady state, evaluated at different times during the study, were observed. For both the Prior OD and Switch groups, the VWF:RCo C_{max} remained stable throughout prophylactic treatment with rVWF.

No severe allergic reactions or neutralizing antibodies against rVWF or rFVIII have been observed during clinical development. One out of 100 VWD subjects treated with rVWF/vonicog alfa in clinical trials developed proximal deep vein thrombosis (DVT) in the perioperative period after undergoing total hip replacement surgery.

Overall, the data support: a) the safety and efficacy of rVWF and rVWF:rFVIII (ADVATE) for OD treatment and control of bleeding episodes as well as in perioperative management of surgery related bleeding, and b) the efficacy and safety of rVWF when used for regular prophylactic treatment in adults diagnosed with VWD.

Please see Section 5 of the IB for further details on clinical studies of rVWF.

2.2.2.2 Ongoing Studies

One other Phase 3 study is ongoing: Phase 3 Study 071102, investigating the efficacy and safety of rVWF in the treatment and control of bleeding episodes and in elective and emergency surgeries, and the PK of rVWF in children diagnosed with severe VWD.

2.3 Study Rationale

The purpose of this Phase 3b continuation study is to evaluate the long-term safety and hemostatic efficacy of rVWF (vonicog alfa) prophylaxis in adult and pediatric/adolescent (age 12 to <18 years) subjects with severe VWD with the option of once weekly dosing, and further assess the safety and efficacy of rVWF in OD treatment of bleeding episodes, and in perioperative management of surgical bleeding (if/when surgical treatment is required for a subject already participating in this study).

2.4 Population to be Studied

Up to 71 pediatric/adolescent and adult subjects with severe VWD (including at least 5 newly enrolled subjects with type 3 VWD on prophylaxis regimen) will be included, composed of: a) up to 22 adult subjects transitioning from Study 071301; b) up to 34 pediatric/adolescent subjects transitioning from Study 071102; c) at least 7 up to 15 newly enrolled adult and pediatric/adolescent (aged 12 to <18 years) subjects who have been receiving VWF products for OD treatment. 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 5.1) and none of the exclusion criteria (see Section 5.2).

2.5 Benefit/Risk Assessment

The benefit for the individual subject is anticipated to outweigh the potential risks of rVWF during this Phase 3b clinical study. Both adult and pediatric/adolescent (aged 12 to <18 years) subjects may benefit from a product that may prevent bleeding episodes by infusions at frequencies as low as once a week and minimizes excessive FVIII administration.

Variations in VWF multimeric composition may lead to variability with respect to treating or preventing bleeds in VWD patients, especially mucosal bleeds with unpredictable efficacy outcomes. The sponsor's rVWF product consistently contains ultra-large von Willebrand Factor (ULVWF) multimers due to the fact that the product has not been exposed to ADAMTS13. The initial presence of these ULVWF multimers, which are subsequently cleaved by the patient's endogenous ADAMTS13, may result in improved platelet and collagen binding and may therefore carry an increased risk of thrombosis. In contrast, these ULVWF multimers may provide more predictable treatment outcomes. By using a recombinant product, the risk of contamination with blood-borne viruses or variant Creutzfeldt-Jakob Disease associated with the use of products of human or animal origin has been virtually eliminated. As with any IV protein product, allergic-type hypersensitivity reactions may occur, as well as neutralizing antibodies to VWF.

In summary, the benefits outweigh the potential risks of rVWF administration at this stage of product development. The key societal benefit is a better understanding of advanced treatment options for VWD patients undergoing surgical procedures and enhanced product availability.

Please refer to the IB for a detailed benefit/risk assessment of rVWF.

Always refer to the latest version of the rVWF IB for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, PK, efficacy, and safety of rVWF.

2.6 Compliance Statement

This study is conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (Integrated Addendum to ICH E6[R1]: Guideline for Good Clinical Practice E6[R2] Current Step 4 version, 9 November 2016), Title 21 of the US Code of Federal Regulations (US CFR), in conjunction with Regulation (European Union [EU]) No 536/2014, the EU Directives (2001/20/EC; 2001/83/EC; 2005/28/EC), and applicable national and local regulatory requirements.

The responsibilities of the study sponsor and investigator(s) are described fully in Appendix 1.

3. OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

- To evaluate the efficacy of rVWF (vonicog alfa) prophylaxis based on the annualized bleeding rate (ABR) of spontaneous (not related to trauma) bleeding episodes in adult and pediatric/adolescent (aged 12 to <18 years) subjects during the first 12 months on study treatment.

3.1.2 Secondary Objectives

- To evaluate the long-term safety of rVWF (vonicog alfa) in adult and pediatric subjects as assessed by AEs including thrombogenicity, hypersensitivity, and immunogenicity, as well as by vital signs and clinical laboratory parameters
- To evaluate the efficacy of rVWF (vonicog alfa) prophylaxis in adult and pediatric/adolescent (aged 12 to <18 years) subjects while enrolled in the study
- To evaluate the efficacy of different dose regimens for prophylactic treatment in adult and pediatric/adolescent (aged 12 to <18 years) subjects
- To assess the efficacy of rVWF (vonicog alfa) for OD treatment of bleeding episodes (spontaneous and traumatic) in adult and pediatric subjects

3.1.3 Exploratory Objectives

In adult and pediatric subjects treated with rVWF:

- To obtain additional data on the efficacy of perioperative bleeding management with rVWF (vonicog alfa) if surgery is required
- To assess pharmacokinetics (PK) and pharmacodynamics (PD) of rVWF (vonicog alfa) and to monitor incremental recovery (IR) of rVWF (vonicog alfa) over time in adult and pediatric subjects
- To assess health-related Quality of Life (HRQoL) data, treatment satisfaction and health resource utilization over time for subjects receiving rVWF (vonicog alfa) prophylaxis.

3.2 Study Endpoints

Table 11. Objectives and Endpoints

Objective	Endpoint(s)
Primary	
To evaluate the efficacy of rVWF (vonicog alfa) prophylaxis based on the ABR of spontaneous (not related to trauma) bleeding episodes in adult and pediatric/adolescent (aged 12 to <18 years) subjects during the first 12 months on study treatment	**Efficacy of Prophylaxis:** • Spontaneous ABR during prophylaxis treatment with rVWF (vonicog alfa) based on the data collected during the first 12 months on study treatment.
Secondary	
To evaluate the long-term safety of rVWF (vonicog alfa) in adult and pediatric subjects as assessed by AEs including thrombogenicity, hypersensitivity, and immunogenicity, as well as by vital signs and clinical laboratory parameters	**Safety:** • AEs/SAEs: incidence, severity, causality • Occurrence of thromboembolic events • Occurrence of hypersensitivity reactions • Immunogenicity a. Development of neutralizing antibodies (inhibitors) to VWF and FVIII b. Development of total binding antibodies to VWF and FVIII c. Development of binding antibodies to CHO proteins, mouse IgG and rFurin • Clinically significant changes in vital signs and clinical laboratory parameters relative to baseline
To evaluate the efficacy of rVWF (vonicog alfa) prophylaxis in adult and pediatric/adolescent (aged 12 to <18 years) subjects while enrolled in the study To evaluate the efficacy of different dose regimens for prophylactic treatment in adult and pediatric/adolescent (aged 12 to <18 years) subjects	**Efficacy of Prophylaxis:** • Spontaneous ABR under prophylactic treatment with rVWF (vonicog alfa) while enrolled in the study • Categorized weekly number of infusions defined as 1, 2, or ≥3 during prophylactic treatment with rVWF (vonicog alfa) • Categorized spontaneous ABR defined as 0, 1 to 2, 3 to 5, or >5 bleeding episodes during rVWF (vonicog alfa) prophylaxis • Time to first bleeding event under each prophylaxis regimen • Spontaneous ABR by location of bleeding (GI, epistaxis, joint bleeding, menorrhagia, oral, muscle and soft tissue, etc.) while on 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 • Transfusion free maintenance of hemoglobin and ferritin levels over time

Table 11. Objectives and Endpoints

Objective	Endpoint(s)
To assess the efficacy of rVWF (vonicog alfa) for OD treatment of bleeding episodes (spontaneous and traumatic) in adult and pediatric subjects	**Efficacy of the Treatment of Bleeding Episodes:** • Overall hemostatic efficacy rating at the resolution of bleed with respect to the treatment of bleeding episodes for the initial 12 months on study treatment • Number of infusions of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) utilized to treat bleeding episodes while enrolled in the study • Weight-adjusted consumption of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) per bleeding episode while enrolled in the study
Exploratory	
To obtain additional data on the efficacy of perioperative bleeding management with rVWF (vonicog alfa) if surgery is required	**Efficacy of Perioperative Management of Bleeding, if Surgery is Needed:** For the first 12 months on study treatment (except for the weight-adjusted dose, which is followed for the entire study period) • 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 • Overall assessment of hemostatic efficacy by the Investigator 24 hours after the last perioperative infusion of rVWF (vonicog alfa) or at day 14 post operation, whichever occurs first • Daily intra- and postoperative weight-adjusted dose of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) through postoperative day 14
To assess PK and PD of rVWF (vonicog alfa) and to monitor incremental recovery of rVWF (vonicog alfa) over time in adult and pediatric subjects	**Pharmacokinetic Endpoints:** • PK parameters including initial assessment for Cohort 4 and EOS steady-state assessment for Cohorts 1 to 4: IR, $T_{1/2}$, MRT, $AUC_{0-\infty}$, AUC_{0-96h}, C_{max}, T_{max}, V_{ss} and CL for VWF:RCo, VWF:Ag, and VWF:CB. The corresponding PD of rVWF (vonicog alfa) as measured in FVIII activity (FVIII:C) will be assessed using C_{max}, T_{max}, and AUC_{0-96h}. • IR over time for the first 12 months prophylaxis for all subjects in prophylactic Cohorts 1, 2, 3, and 4 at the scheduled follow-up visits
To assess HRQoL data, treatment satisfaction and health resource utilization over time for subjects receiving rVWF (vonicog alfa) prophylaxis	**Health Economics and Outcomes Research Endpoints:** At baseline, 6, and 12 months, and EOS visit: • HRQoL as assessed using Questionnaires: a. for adults (≥18 years of age): EQ-5D-3L, SF-36, and V-WIQ b. for pediatric subjects aged 2 to <18 years at Screening: PedsQLTM and parent proxy version o PedsQLTM Teen report (ages 13 to 17) (23 items) o PedsQL™ Child report for children (ages 8 to 12) (23 items) o PedsQLTM Parent report for young children (ages 5 to 7) (23 items)

Table 11. Objectives and Endpoints

Objective	Endpoint(s)
	○ PedsQLTM Parent report for toddlers (ages 2 to 4) (21 items) EQ-5D-Y for subjects ≥7 years (parent-proxy version for ages 4 to <7 years) Pain: VAS • Treatment Satisfaction: TSQM-9 (baseline assessment is not applicable for Cohort 4 newly enrolled subjects) • Health resource utilization and productivity data, including number and duration of hospitalizations, emergency room visits, urgent care physician visits and days missed from school or work.

ABR=annualized bleeding rate; AE=adverse events; SAE=serious adverse event; EOS=end of study; FVIII=Factor VIII; rFVIII=recombinant Factor VIII; CHO=Chinese hamster ovary; IgG=immunoglobulin G; rVWF=recombinant von Willebrand factor; GI=gastrointestinal; OD=on demand; PD=pharmacodynamic; PK=pharmacokinetic; IR=incremental recovery; $T_{1/2}$=terminal half-life; MRT=mean residence time; $AUC_{0-\infty}$=area under the concentration versus time curve from 0 to infinity; AUC_{0-96h}=area under the concentration versus time curve from 0 to 96 h; C_{max}=maximum concentration; T_{max}=time to reach C_{max}; V_{ss}=volume of distribution at steady state; CL=clearance; VWF:Ag=von Willebrand factor antigen; VWF:RCo=von Willebrand factor Ristocetin cofactor activity; VWF:CB=von Willebrand factor collagen binding activity; FVIII:C=FVIII activity; HRQoL=health-related quality of life; SF-36=Short Form (36) Health Survey; EQ-5D=EuroQoL five-dimension questionnaire; V-WIQ=von Willebrand impact questionnaire; PedsQL™=pediatric quality of life inventory™; VAS=visual analog scale; TSQM-9= The nine-item Treatment Satisfaction Questionnaire for Medication

4. STUDY DESIGN

4.1 Overall Design

This is a phase 3b, prospective, open-label, uncontrolled, non-randomized, multicenter study evaluating long-term safety and efficacy of rVWF (vonicog alfa) for prophylaxis and on-demand (OD) treatment of bleeding episodes in pediatric and adult subjects with severe VWD. The study plans to include cohorts as summarized below:

Prophylactic treatment arm cohorts:

1. Adult subjects transitioning from the phase 3 Prophylaxis study (Study 071301) who will remain on the same prophylactic dose as in Study 071301
2. Adult subjects transitioning from Study 071301 with no clinically significant bleeding episode for the past 6 months who will start this phase 3b study at a lower dose/frequency compared to the dose received in Study 071301
3. Pediatric/adolescent subjects aged 12 to <18 years transitioning from the phase 3 pediatric study (Study 071102) who switch from receiving OD treatment to receiving once weekly or twice weekly prophylaxis
4. Newly enrolled adult and pediatric/adolescent (aged 12 to <18 years) subjects switching from OD treatment with VWF products, starting once weekly prophylaxis with rVWF (vonicog alfa) in this phase 3b extension study

On-demand treatment arm cohorts:

5. Pediatric subjects of all ages from Study 071102 who will continue with receiving OD treatment
6. Adult subjects from Study 071301 who will switch back from prophylactic treatment to OD treatment

Adult subjects transitioning from Study 071301 who agreed to continue prophylactic treatment were given an opportunity to have their prophylactic dose re-evaluated at the beginning of this study; if a subject experienced no bleeding episode over the last 6 months of their prophylactic treatment in Study 071301, the subject might have been given a reduced dosage in this study (at the discretion of the principal investigator based on the detailed guidance provided in the protocol) (Cohort 2). Otherwise subjects continued with the prophylactic treatment regimen from Study 071301 (Cohort 1), which was expected to be 50 (±10) IU/kg rVWF:RCo twice weekly for the majority of subjects, at the beginning of this study.

Pediatric/adolescent subjects aged 12 to <18 years transitioning from the pediatric study 071102 who were considered eligible by the investigator for switching to prophylaxis might have selected to go on prophylactic treatment with rVWF (vonicog alfa) (Cohort 3) at a dose of either 50 (±10) IU/kg rVWF:RCo once weekly or twice weekly, based on the investigator's assessment and recommendation. Dosage might have been individualized within this range and, in consultation with the sponsor, increased up to 80 IU/kg if considered necessary to assure effective prophylaxis, based on: a) subject's available historical PK data; b) type and severity of bleeding episodes the subject has experienced; c) monitoring of appropriate clinical and laboratory measures for the subject.

Newly enrolled adult and pediatric/adolescent (aged 12 to <18 years) subjects (Cohort 4) will all be initially assigned to a prophylactic regimen of 50 (±10) IU/kg rVWF:RCo once per week with rVWF (vonicog alfa) if they are considered eligible and recommended by the investigator to receive prophylactic regimen and they choose to agree with the investigator's recommendation. The starting dose, after consultation with the Sponsor, can be increased up to 80 IU/kg if considered necessary to assure effective prophylaxis.

The remaining pediatric subjects (aged <18 years) from all age cohorts in Study 071102 who will not transition to prophylaxis and will continue to receive OD treatment (Cohort 5) and adult subjects from 071301 who were assigned (based on medical assessment and/or subject's individual preference) to switch back to OD regimen (Cohort 6) will receive rVWF (vonicog alfa) as OD treatment in this study.

For all subjects on prophylactic treatment (Cohorts 1 to 4), dose and/or dose frequency will be increased based on bleeding episode dose-escalation criteria (please refer to Section 6.2.2.1.2 in for dose escalation details).

For all cohorts, during the entire study observation period, any bleeding episodes requiring substitution therapy with VWF concentrate will be treated with rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa). If surgery is needed, subjects will receive rVWF (vonicog alfa), with or without ADVATE (rFVIII, octocog alfa), for management of perioperative bleeding; however, for pediatric subjects aged <18 years, if/when they need surgical intervention/procedures during their participation in this study, the assessment whether they can be treated with the IP for the peri-operative management of bleeding requires consultation with the study medical monitors (also see Section 6.2.2.3).

Once assigned, the cohort number of a subject will remain unchanged during the study. Change of treatment regimen will not result in switch of cohorts.

Minimum observation time for this study is 12 months and after this initial 12-month period, subjects will continue to be enrolled in the study until rVWF (vonicog alfa) is commercially available in their respective countries, or until subjects have been treated in the study for a maximum of 3 years, whichever occurs first. An interim analysis is planned once the subjects in the prophylactic treatment arms complete the initial 12 months on study treatment. Additional interim analyses may be performed as needed to support submissions to health authorities.

4.2 Scientific Rationale for Study Design

The phase 3b extension/continuation study with rVWF/vonicog alfa is designed to:

- Explore additional doses/dose intervals for prophylaxis indication (eg, once weekly dosing)
- Allow for prophylaxis in pediatric/adolescent subjects (Cohort 4)
- Generate long term safety and efficacy data in adult and pediatric subjects

4.3 Justification for Dose

Efficacy of 40-60 IU/kg for prophylactic treatment was evaluated in adult VWD patients in a phase 3 study (071301). Based on experience with plasma derived VWF products and the relatively long MRT for rVWF, it is of significant interest and relevance to evaluate a wider dosing range, including once weekly dosing.

4.4 Duration of Subject Participation and Study Completion Definition

The subject's maximum duration of participation is expected to be 3 years. The study will be completed in approximately 7 years.

The Study Completion Date is defined as the date on which the last subject in the study completes the final protocol-defined assessment(s). This includes the follow-up visit or contact, whichever is later (refer to Section 8.3.7 for the defined follow-up period for this protocol).

4.5 Sites and Regions

The study will be conducted at 55 study sites in the US, Canada, Turkey, Russian Federation, Ukraine, and EU.

4.6 Randomization and Blinding

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

4.7 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 (e.g., underlying or concurrent condition, use of concomitant medication, subject's medical history, etc.):

1. Two subjects develop a life-threatening or fatal thromboembolic event
2. Two subjects develop life-threatening or fatal severe hypersensitivity reactions (e.g., anaphylaxis)
3. Any subject develops acute hepatic failure
4. Two subjects develop rVWF neutralizing antibodies that are considered clinically significant by the investigators and are associated with significant decrease of efficacy or serious adverse reactions.

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

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.

4.8 Global Health Emergencies and Clinical Trial Continuity

Global health emergencies, such as the COVID-19 pandemic, present significant logistical challenges for many clinical sites around the world. Variable restrictions are being placed on site resources and operations and on an individual participant's ability to attend clinic visits. In some places, medical visits are occurring, and in others, research clinics are operating with only emergency staff.

Because of these challenges, additional measures and procedures may need to be adopted to protect participant safety and to ensure that participants do not experience gaps in the conduct of the study.

This protocol includes measures approved for implementation within this clinical trial to protect participant safety and to ensure the integrity of the clinical trial, as a result of COVID-19 only. These measures may be implemented in accordance with any requirements and expectations set out by local Independent Review Boards/Independent Ethics Committees and National Competent Authorities, as necessary. In order to maintain the scientific integrity of the study, and adhere to updated guidance from regulators, procedures have also been put into place to ensure that the actions taken to mitigate the impact of COVID-19 are well documented in the trial database.

These specific measures do not apply for subject management issues that are unrelated to a documented impact from a public health emergency, such as the COVID-19 pandemic.

5. STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed.

5.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below.

Subjects who have completed Study 071301 or Study 071102 (or subjects who have completed the surgery in Study 071102 and want to continue to receive OD treatment) and are willing to immediately transition into this study, must meet the following 2 criteria to be eligible for this study:

1. If female of childbearing potential, has a negative blood/urine pregnancy test at screening and agrees to employ highly effective birth control measures (including sterilization, implant, intra-uterine device (IUD), correct and consistent use of hormonal contraception, and abstinence) for the duration of the study.
2. Subject and/or legally authorized representative is willing and able to comply with the requirements of the protocol.

New subjects (Cohort 4) who meet the above 2 and **ALL** the following additional criteria are eligible for this study:

3. Subject has a documented diagnosis of severe VWD (baseline VWF:RCo <20 IU/dL) with a history of substitution therapy with VWF concentrate required 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).

Diagnosis is confirmed by genetic testing and multimer analysis, documented in patient history or at screening.

4. Subject has been receiving OD therapy with VWF products for at least 12 months, and prophylactic treatment is recommended by the investigator.
5. Subject has ≥3 documented spontaneous bleeds (not including menorrhagia) requiring VWF treatment during the past 12 months.

6. Subject has available records that reliably evaluate type, frequency, and treatment of bleeding episodes for at least 12 months preceding enrollment; up to 24 months of retrospective data should be collected if available.
7. Subject is ≥12 years old at the time of screening and has a body mass index ≥15 but <40 kg/m^2.

5.2 Exclusion Criteria

The subject will be excluded from the study if any of the following exclusion criteria are met.

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 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 Bethesda units (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 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 human immunodeficiency virus (HIV) positive with an absolute Helper T cell (CD4) count <200/mm^3.
8. 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, but not limited to 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) or liver cirrhosis classified as Child-Pugh class B or C.
9. The subject has been diagnosed with renal disease, with a serum creatinine (CR) level ≥2.5 mg/dL.
10. The subject has a platelet count <100,000/mL at screening (for subjects with type 2B VWD, platelet count(s) at screening will be evaluated taking into consideration historical trends in platelet counts and the Investigator's medical assessment of the patient's condition).

11. 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 (or assent, if appropriate).
12. The subject is pregnant or lactating at the time of enrollment.
13. The subject has cervical or uterine conditions causing menorrhagia or metrorrhagia (including infection, dysplasia).
14. 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.
15. The subject has a progressive fatal disease and/or life expectancy of less than 15 months.
16. For new OD subjects, the subject is scheduled for a surgical intervention.
17. The subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
18. 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.
19. 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

Only for Cohort 4, if the subject presents with an acute bleeding episodes or acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, and non-seasonal asthma) the screening visit will be postponed until the subject has recovered. For all other subjects, end-of-study (EOS) visit for 071102 or 071301 will be completed per protocol and the completed EOS in Study 071102 or 071301 will also serve as the screening visit for this continuation study (SHP677-304).

5.3 Restrictions

No dietary or activity restrictions are associated with this study.

5.4 Reproductive Potential

5.4.1 Female Contraception

Sexually active females of childbearing potential should use an acceptable form of contraception. Females of childbearing potential must be advised to use acceptable contraceptives throughout the study period and for 30 days following the last dose of investigational product. If used, hormonal contraceptives should be administered according to the package insert. Any female of childbearing potential who is not currently sexually active must agree to use acceptable contraception, as defined below, if she becomes sexually active during the study and for 30 days following the last dose of investigational product.

Female children and adolescent subjects:

- Females of childbearing potential with a negative urine and/or serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at the screening visit.
- Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception include the following birth control methods that may be considered as highly effective according to guidelines of Clinical Trial Facilitation Group (refer to Appendix 4):

- 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
    - intrauterine device (IUD)
    - intrauterine hormone-releasing system (IUS)
    - bilateral tubal occlusion
    - vasectomized partner
    - sexual abstinence

6. STUDY INTERVENTION

6.1 Investigational Product(s)

6.1.1 Identity of Investigational Product(s)

rVWF (vonicog alfa) will be provided in single boxes with 2 glass vials, with one vial containing the lyophilized rVWF, and the second vial containing the diluent. Additional information is provided in the current rVWF 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 in lyophilized form which may be stored at room temperature (up to 30°C [86°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. If the product was stored in the refrigerator, after removal of the product from the refrigerator, it 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.

rFVIII (Recombinant Factor VIII, octocog alfa /ADVATE): rVWF (vonicog alfa) may be used, as deemed necessary by the Investigator, in combination with rFVIII (octocog alfa /ADVATE) which 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.

6.1.2 Blinding the Treatment Assignment

Not applicable.

6.2 Administration of Investigational Product

Following reconstitution, rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) 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 reconstituted solution in the syringe should be clear, colorless and free from particles. It is not uncommon for a few flakes or particles to remain in the product vial after reconstitution. The filter included in the Mix2Vial device removes those particles completely. Filtration does not influence dosage calculations. The solution filtered into the syringe to be administered, 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 can only be allowed for pediatric subjects with a potential concern of exceeding the dose range for study treatment per protocol.

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, if/when needed, 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.

If/when ADVATE use is considered necessary, the final dose of rVWF (vonicog alfa): ADVATE (rFVIII, octocog alfa) should be at a ratio of (1.3± 0.2):1.

6.2.1 Allocation of Subjects to Treatment

This is a Phase 3b, prospective, open-label, uncontrolled, multi-center study. The actual treatment given to individual subjects is determined by the inclusion/exclusion criteria and the

Investigator's medical/clinical assessment of the subject's condition and response to previous treatment regimen(s).

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

6.2.2 Dosing

Recombinant von Willebrand factor (rVWF, vonicog alfa) will be administered IV.

6.2.2.1 Prophylactic Treatment

The individualized prophylaxis dose assignment will have to be agreed with the sponsor in advance. Agreement will be documented by sponsor signature and include the rationale for dose selection.

a. **Cohort 1**: Adult subjects from Study 071301 who will continue with the same prophylactic treatment regimen from Study 071301, which is expected to be 50 (±10) IU/kg rVWF:RCo twice weekly for the majority of subjects.

b. **Cohort 2**: Adult subjects from Study 071301 who experienced no clinically significant bleeding episode over the past 6 months and who elected to follow the recommendation by the investigator to start prophylactic treatment in this study with reduced dosing frequency and/or change of dose per infusion.

c. **Cohort 3**: Pediatric/adolescent subjects aged 12 to <18 years who:

   - transition from Study 071102 with at least 3 bleeding episodes (not including menorrhagia) that required treatment with a VWF product and occurred over the past 12 months, and
   - are considered eligible for prophylactic treatment per investigator's medical/clinical assessment

   may receive rVWF (vonicog alfa) for prophylaxis if they elect to go on prophylactic treatment following the recommendation by the investigator.

The dosage selected may be either:
a) Twice weekly 50 (±10) IU/kg rVWF:RCo, or
b) Once weekly 50 (±10) IU/kg rVWF:RCo
based on the investigator's assessment and recommendation. Dosage may be individualized within this range, in consultation with the sponsor, increased up to 80 IU/kg if considered necessary to assure effective prophylaxis, based on:

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

d. **Cohort 4:** Newly enrolled adult and pediatric/adolescent (aged 12 to <18 years) subjects who:

- were previously treated with VWF products for bleeding episodes OD, with at least 3 bleeding episodes (BE), excluding menorrhagia, that occurred over the past 12 months, and
- are considered eligible for prophylactic treatment based on the investigator's medical/clinical assessment

will receive rVWF (vonicog alfa) once weekly 50 (±10) IU/kg rVWF:RCo. Dosage may be individualized within this range and, in consultation with the sponsor, increased up to 80 IU/kg if considered necessary to assure effective prophylaxis, based on:

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

6.2.2.1.1 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 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 OD treatment and to subjects rolling over from adult prophylaxis regimen. 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.

Subjects who receive home treatment may receive IP through a direct-to-patient (DTP) process, and the site will follow-up with the subject or, for pediatric subjects, the subject's parent(s) or legally authorized representative. When utilizing DTP, the investigator remains responsible for ensuring the safety of subjects and the dispensation of the IP. A Subject Guideline detailing all instructions and information listed above will be provided to each subject.

6.2.2.1.2 Dose Escalation

For all subjects on prophylaxis, if escalation criteria are ever met during the study, dose escalation, per protocol, will be performed. Dose escalations (not exceeding the upper limit of 80 IU/kg rVWF:RCo per dose) 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 location but, in general, involve one significant breakthrough bleeding episode despite the subject being compliant with scheduled prophylactic treatment. For subjects who require a dose escalation due to a breakthrough bleed, preferentially, the frequency should be kept the same but the dose (IU/kg VWF:RCo per infusion) should be increased up to 80 IU/kg VWF:RCo. Based on the subject's bleeding history, the investigator' clinical judgement and the pharmacokinetic data (if available), dose escalation by increasing the dose frequency should be considered. Any increase in dose or dose frequency should be done in consultation with the Sponsor. Table 12 presents the criteria for dosing escalation per each bleeding location.

All dose adjustments need to be done in consultation with the sponsor.

Table 12. Criteria for Prophylactic Dose Escalation Specific to Each Bleeding Indication

	Schedule A	Schedule B
Joint bleeding	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial), once or twice per week (depending on schedule at the start of study for each individual subject). In the event a spontaneous joint bleeding episode occurs while on this regimen, the subject may escalate to up to 80 IU/kg per dose, or if clinically indicated, go directly to Schedule B following its resolution	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) per dose with an increase in dose frequency of 1 dose per week. Each dose may be further increased up to 80 IU if clinically indicated.
GI bleeding	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) once or twice per week (depending on schedule at the start of study for each individual subject). 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 per dose, or if clinically indicated, go directly to Schedule B following its resolution	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) per dose with an increase in dose frequency of 1 dose per week. Each dose may be increased up to 80 IU/kg if clinically indicated.
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) once or twice per week (depending on schedule at the start of study for each individual subject). The subject will escalate to up to 80 IU/kg per dose, or if clinically indicated, to Schedule B (e.g. 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) per dose with an increase in dose frequency of 1 dose per week. Each dose may be further escalated to 80 IU/kg if clinically indicated.
Oral and Other Mucosa	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) once or twice per week (depending on schedule at the start of study for each individual subject). The subject will escalate to up to 80 IU/kg per dose or, if clinically indicated go to Schedule B (e.g. 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) per dose with an increase in dose frequency of 1 dose per week. Each dose may be increased to 80 IU/kg if clinically indicated

Table 12. Criteria for Prophylactic Dose Escalation Specific to Each Bleeding Indication

	Schedule A	Schedule B
Muscle and Soft Tissue	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) once or twice per week (depending on the schedule at the start of study for each individual subject). In the event a spontaneous bleeding episode occurs while on this schedule, the subject will escalate to up to 80 IU/kg per dose or, if clinically indicated go to Schedule B following its resolution.	50 ± 10 IU VWF:RCo/kg (rounded up to the nearest vial) per dose with an increase in dose frequency of 1 dose per week. Each dose may be increased up to 80 IU/kg if clinically indicated.

GI = gastrointestinal; IU = International Unit; PBAC = Pictorial Blood Assessment Chart; VWF:RCo = von Willebrand factor: Ristocetin cofactor.

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 8.4.3.13.1). If a subject experiences a bleed while receiving rVWF (vonicog alfa) 3 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 6.5). If one 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, if a subject routinely infuses IP on Monday and Thursday, in the case he/she misses the Monday time point, he/she 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 then 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 7.2). Any foreseeable or unforeseeable changes to the planned prophylactic dosing regimen due to COVID-19 related constraints should be communicated/reported to the Sponsor and study teams as soon as possible.

6.2.2.2 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% 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± 0.2) : 1 should be administered initially. Subsequent infusions should be with rVWF:RCo 40 to 60 IU/kg with or, in many cases, without

ADVATE (30 to 45 IU/kg, 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 principal investigator (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 >0.3 IU/mL (30%). 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 13.

Table 13. 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

Table 13. rVWF:RCo Dosing Recommendations for the Treatment of Bleeding Episodes Due to VWD

Classification of VWD	Hemorrhage	Dosage (IU VWF:RCo/kg BW)

BW = body weight; CNS = central nervous system; GI = gastrointestinal: IU = international unit;
VWD = von Willebrand disease; VWF:RCo = von Willebrand factor: Ristocetin cofactor

[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.

Dosage and frequency must be individualized based on the subject's weight, VWD type and severity of bleeding episode and monitoring of appropriate clinical and laboratory measures. In general, an initial dose of 40 to 60 IU/kg VWF:RCo is recommended. Depending on the subject's baseline FVIII level, rVWF should be given with or without 30 to 45 IU/kg ADVATE (rFVIII, octocog alfa) (rVWF: rFVIII ratio of 1.3± 0.2 : 1). In cases of major bleeding episodes, a dose of up to 80 IU/kg VWF:RCo may be infused. If necessary, subsequent doses of 40 to 60 IU/kg VWF:RCo will be administered every 8 to 24 hours with or without ADVATE [rFVIII, octocog alfa] (only to be administered if plasma FVIII levels fall below 30 IU/dL during the treatment period) to maintain VWF:RCo and FVIII levels for as long as deemed necessary by the investigator.

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 T1/2 for rVWF (vonicog alfa) was 19.3 hours, with a standard deviation of 10.9 hours.

Variances of up to 10% in dosing are permissible during treatment of bleeding episodes, but especially for the pediatric subjects, 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 13. 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.

6.2.2.2.1 General Instructions for Home Treatment for 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 6.2.2.1.1).

If a subject is not qualified for home treatment, rVWF (vonicog alfa) infusions must be administered at the study site or, due to extraordinary circumstances such as COVID-19, by other health-care providers who are informed/trained about the study treatment and IP administration specifics.

If a roll-over 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. If a new subject screened for eligibility for Cohort 4 experiences a bleeding episode that requires VWF treatment between the screening and the prophylaxis initiation visit, the subject will be treated with his/her standard of care, such as commercial pdVWF/FVIII products.

For Cohort 4 subjects, a washout period of at least 5 days is required prior to rVWF (vonicog alfa) PK infusion at the PK assessment visit. 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.

6.2.2.3 Management of Perioperative 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. Pediatric and adolescent subjects who completed Study 071102 and enrolled in this study to continue receiving on-demand treatment with rVWF or adolescent subject(s) enrolled in this study to start receiving prophylactic treatment with rVWF will be treated with IP to manage surgery/procedure related bleeding if/when they require surgical, invasive or oral/dental procedures if their corresponding age cohort in Study 071102 has been opened to allow enrollment of surgery subjects for the type of surgery/procedure (minor or oral, or major surgeries) required in this study. If the corresponding age cohort in Study 071102 has not been opened for the type of surgery required in this study for pediatric/adolescent subjects, the subject should be treated with standard of care therapies as concomitant treatment. New subjects who have an already scheduled surgical intervention at the time of screening for Cohort 4, are not eligible for participation in the study.

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 IV access devices, removal of small skin lesions, arthroscopy, gastroscopy, colonoscopy or conization.

Oral surgeries comprise extractions of fewer than 3 teeth, if the teeth are non-molars and have no bony involvement.

A summary schedule of visit assessments is included in Table 4 and Table 8.

The dose and frequency of administration of rVWF will be individualized based on the type of surgery, PK results, and VWF and FVIII levels. In general, the dose will be tailored to raise the VWF:RCo concentration to 100% of normal for major surgeries, and to 50 to 60% of normal for minor and oral surgeries.

For subjects undergoing elective surgery, an rVWF priming dose is to be infused 12 to 24 hours prior to surgery in subjects with inadequate levels of FVIII, to allow the endogenous FVIII levels to increase to at least 30 IU/dL (for minor and oral surgery) or 60 IU/dL (for major surgery) before the loading dose of rVWF (vonicog alfa).

For both elective and emergency surgery, an rVWF loading dose should be administered within 3 hours prior to surgery. ADVATE (rFVIII, octocog alfa) may be administered in addition to rVWF (vonicog alfa) in order to raise FVIII:C levels to recommended levels.

If not assessed prior to the preoperative priming dose, an IR may be calculated for subjects undergoing minor and oral 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 (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. As a general guidance, a loading dose of 40 to 60 IU/kg rVWF:RCo should be administered. ADVATE, at a dose of 30 to 45 IU/kg may be infused sequentially, preferably within 10 minutes after the rVWF infusion in subjects whose FVIII plasma levels already are (or are highly likely to be) less than 40 to 50 IU/dL for minor/oral surgery or 80 to 100 IU/dL for major surgery before the initiation of the surgery. At the discretion of the Investigator, the ADVATE dose may be increased in subjects requiring emergency surgery who did not receive a preoperative priming dose.

The peri- and postoperative substitution regimen will be individualized according to PK results; intensity and duration of the hemostatic challenge; and the institution's standard of care. Dosing should be guided by the dosing recommendations and continued until healing is achieved. 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.

6.2.2.4 PK Assessment

For subjects in Cohort 4, the PK dose is 50 (±5) IU/kg rVWF:RCo for the initial PK assessment at the beginning of the study. Additionally, subjects in Cohorts 1-4 will undergo steady state PK assessment at the EOS, and the PK dose is their last scheduled prophylactic dose.

6.2.3 Unblinding the Treatment Assignment

Not applicable.

6.2.4 Dose Modification

Details are in Section 6.2.2.1.

6.3 Labeling, Packaging, Storage, and Handling of Investigational Product

6.3.1 Labeling

Labels containing study information and pack identification are applied to the investigational product(s) container. Details are provided in Section 6.1.1.

6.3.2 Packaging

Details are provided in Section 6.1.1. Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.3.3 Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are administered by the investigator. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Details are provided in Section 6.1.1. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over

a specific time period can be recorded and retrieved as required. Such a device (i.e., certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), e.g., fumigation of a storage room.

6.3.4 Special Handling

Before administration, the reconstituted product has to be brought to room temperature. Storage of rVWF post-reconstitution should be limited to 3 hours at room temperature.

In case large volumes of rVWF are required, it is possible to pool not more than 2 vials of rVWF together. The contents of each reconstituted product can be drawn in a single syringe.

The rVWF FDP (dosage strength: 650 VWF:RCo IU per vial) is reconstituted with a sterile water for injection (SWFI) with a nominal volume of 5 mL and a minimum extractable volume of 5 mL.

The rVWF FDP (dosage strength: 1300 VWF:RCo IU per vial) is reconstituted with a sterile water for injection (SWFI) with a nominal volume of 10 mL (minimum extractable volume of 10 mL). The SWFI is manufactured by Siegfried Hameln GmbH (Germany).

The ADVATE FDP (dosage strength: 500 IU per vial and 1000 IU per vial) is reconstituted with a sterile water for injection (SWFI) with a nominal volume of 2 mL (minimum extractable volume of 2 mL).

If ADVATE is needed in addition to rVWF, sequential administration will be done with rVWF being infused first. Mixing of rVWF and ADVATE is not permitted.

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be

maintained as detailed further in this section, including the situations where home treatment is allowed based on the investigator's judgment following appropriate training provided to the caregiver and/or subject.

The investigator has overall responsibility for administering investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All administered will be documented in the subject's source and/or other investigational product record.

No investigational product stock or returned inventory from a Takeda-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.5 Subject Compliance

The Investigational product will be administered in the study center by the authorized study center staff. The investigator or designee will record the correct dose, date, and time of administration on the Drug Accountability Record. If a subject has qualified for home treatment, then IP may be administered by a healthcare professional trained and qualified by the site investigator.

6.6 Prior and Concomitant Therapy

All non-study medications taken and non-drug therapies received within 30 days prior to the screening visit and through the final study contact (including protocol defined follow-up period) will be recorded on the concomitant medications and non-drug therapies eCRFs.

6.6.1 Prior Treatment

Prior treatment includes all treatment (including but not limited to herbal treatments, vitamins, non-pharmacological treatment such as psychotherapy as appropriate) received from 30 days prior to the screening visit until before the first dose of investigational product. Prior treatment information must be in the subject's source document.

6.6.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the end of the follow-up period, inclusive. Concomitant treatment information must be in the subject's source document.

6.6.3 Permitted Treatment

Adjunctive therapy with the following medications/products can be allowed based on the clear medical necessity per investigator's judgment, or when/if additional rVWF and/or rFVIII dose(s) are administered and determined to be not sufficient in establishing hemostasis during a bleeding episode:

- Antifibrinolytics (e.g., tranexamic acid, epsilon amino caproic acid) or topical hemostats (e.g. human fibrin glue) 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. Antifibrinolytics may also be used in conjunction/concomitantly with rVWF/vonicog alfa.
- Emergency use of a VWF concentrate other than rVWF (vonicog alfa) may be permissible under certain circumstances (see Section 6.2.2.2.1).

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

6.6.4 Prohibited Treatment

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

- immunomodulatory drugs, excluding topical treatment (e.g., ointments, nasal sprays)
- another investigational and/or interventional drug

The following medications are not allowed within 5 days of the PK study infusion or surgery:

- drugs with antiplatelet activity (e.g. dextran, non-steroidal anti-inflammatory drugs and acetylsalicylic acid compounds);
- DDAVP
- cryoprecipitate or Factor concentrate containing VWF and/or FVIII other than rVWF/vonicog alfa and/or rFVIII.

Treatments not listed above are considered allowable.

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.

7. DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

If investigational product is discontinued, regardless of the reason, the evaluations listed for End of Study Visit will be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified evaluations at EOS Visit. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for discontinuation, date of discontinuation of the investigational product, and the total amount of investigational product administered must be recorded in the source documents.

Subjects who discontinue will not be replaced.

7.2 Reasons for Discontinuation

The reason for discontinuation must be determined by the investigator and recorded in the subject's source document. If a subject is discontinued for more than 1 reason, each reason should be documented in the source and the most clinically relevant reason should be indicated.

Reasons for discontinuation include, but are not limited to:

- Adverse event
- Protocol deviation
- Withdrawal by subject
- Lost to follow-up
- Lack of efficacy
- Other (eg, pregnancy)

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.

If a subject is withdrawn from study participation due to personal concerns related to public health emergencies such as COVID-19 (other than an AE related to the emergency), this should be specified as the reason for subject withdrawal in the eCRF. Investigators should use the "Other" discontinuation reason and specify the relation to the public health emergency. Any protocol deviations surrounding public health emergencies, such as the COVID-19 pandemic,

will be clearly identified within the protocol deviation description and summarized separately in the clinical study report.

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 upper limit of normal (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. Withdrawal from the Study

A subject may withdraw from the study at any time and for any reason without prejudice to his/her future medical care by the physician or at the institution, or may be withdrawn at any time at the discretion of the investigator or sponsor (e.g., in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject with the medical monitor when possible.

7.3 Subjects "Lost to Follow-up" Prior to the Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject who is lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that the subject return to the site for final safety evaluations and return any unused investigational product.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 Informed Consent and Enrollment

Prior to performing any trial assessments that are not part of routine medical care for the subject, the investigator will obtain written informed consent as described in Appendix 1.5. Any patient who provides informed consent (i.e., signs and dates the informed consent form (ICF)) is considered a subject enrolled in the study.

8.2 Subject Identification Code (SIC)

The following series of numbers will comprise the SIC: protocol identifier (e.g., 071304) 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 071304-020003. 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.

8.3 Study Schedule

The overall study design is illustrated in Figure 1 and Figure 2. Details on the procedures to be performed at each study visit, including screening, are provided in Table 1, Table 2, Table 3, Table 5, Table 6 and Table 7. Study assessments are detailed in Section 8.4.

In acknowledgement of hospital, local, state, or national government restrictions or other site related factors caused by unavoidable circumstances (eg, COVID-19 pandemic) which may prevent Investigators from conducting the study according to the Schedule of Assessments at the clinical study site, Investigators may seek approval from the Medical Monitor(s) to continue subjects in the study despite departure from the Schedule of Assessments. Investigators are expected to evaluate the impact to the safety of the study participants and site personnel for subjects to continue the study assessments/procedures as previously planned and consider rescheduling/replanning of the visits and assessments/procedures in consultation with the study Medical Monitor(s). In evaluating such requests, the Medical Monitor(s) will give the highest priority to the safety and wellbeing of the subjects. For subjects that are impacted, any procedures not conducted per the original study plan will be documented in the study records including the cause for the change(s) made.

When approval is given for a subject to miss an in-person study visit, a study site physician will speak directly with the subject, or if applicable, the subject's parent(s)/legally authorized representative(s) by telephone or other medium (eg, a computer-based video communication) during each visit window to assess subject's safety and overall clinical status. During this contact, the study site physician or other qualified site staff should also, at a minimum, conduct the following assessments: AE collection, concomitant medication documentation. Other study assessments may be performed remotely as applicable, and may involve audio or video recording. Additionally, sites may send site staff to subjects' residences to conduct study assessments contingent upon local regulations. Assessments that cannot be completed during the protocol specified window will be considered missing data, such departures will be recorded in the study records including the reason for the missed assessment and will be considered protocol deviations. Alternatively, sites may seek approval to extend the visit window in order to conduct an on-site visit.

8.3.1 Screening Visit

In order to thoroughly assess a potential subject's condition and ability to fully comply with the requirements of the protocol, a joint pre-screening medical evaluation of potential subjects shall be conducted by the Investigator and the Study Medical Monitors (including Sponsor's and CRO's Medical Monitors) prior to performing any screening tests and/or procedures. One aspect of this pre-screening medical evaluation is to assess the overall condition of patients with respect to the required blood volume to be collected for the test samples necessary for screening and baseline (including PK) assessments and procedures. General recommendations provided in the review article published by The Bulletin of the World Health Organization (Howie 2011) will be taken into account as well as the guidelines by the Investigator's institution and other parameters pertaining to each individual patient under consideration for screening, to ensure patient safety and compliance with the criteria provided in this protocol and the study consent forms. A summary of the discussion/pre-screening medical evaluation including Study Medical Monitors' signatures will be documented by the CRO's Study Medical Monitor.

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, flulike 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, genetics, multimeric pattern and HRQoL, must be repeated to reconfirm eligibility. 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 receive an e-diary at the beginning of their study participation that will include IP infusion logs

(including the regular prophylactic treatment infusions), bleeding episodes and treatment, AEs, concomitant medications and treatments, and patient reported outcomes (including quality of life and health resource use data). Multimer analysis and VWD gene mutation analysis should be performed at screening if not available in the subject's medical history. If multimer analysis and VWD gene mutation analysis cannot be performed at screening, given the subject meets all eligibility criteria, these assessments may be performed during the subject's participation in the study and as soon as possible.

The study site is responsible for maintaining a screening and enrollment log that includes all subjects who provided informed consent/assent. The log also will serve to document the reason for screening failure. If a subject does not satisfy all screening criteria, the same subject may be re-screened at a later date. A complete or partial re-screen may also become necessary at the discretion of the investigator or sponsor. All screening data will be collected and reported in CRFs, regardless of screening outcome. For the purpose of analysis, only the data from the most recent screening visit will be used. 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.

Subjects who fail screening due to a single laboratory test result which does not meet eligibility criteria may have that laboratory test repeated at the discretion of the Investigator. This will include a repeat of only the failed assessment; complete rescreening will not be necessary. In these cases, a new SIC is not required, the subjects will maintain their original SIC. The repeat of a screening value is allowed once. A repeat assessment must take place within 42 days of the initial screening for any subject requiring repeat of a screening assessment. If this timeframe is exceeded, then all screening assessments must be repeated and the subject assigned a new SIC.

Subjects transitioning from 071301 or 071102 can use the end of study assessments in their previous rVWF study for screening visit assessments in this extension study. Any additional required screening assessments will be performed the same day. Therefore, whenever possible the Screening visit should coincide with the EOS visit of the previous rVWF study. However, if this is not possible, a small gap between the Screening visit and the EOS of the prior study may be allowed upon consultation with the Sponsor. Subjects' eligibility should be confirmed no later than 42 days after the end of study visit in their prior study, which is to also serve as the continuation study's screening visit. Additionally, transitioning subjects will receive the first prophylactic IP treatment either as part of the IR determination of the EOS visit of the previous rVWF study (when the Screening visit coincides with the EOS visit of the prior study) or at the screening visit of this continuation study (when the 2 visits are not on the same day).

For the transitioning/roll-over subjects from studies 071102 and 071301, in the event of a subject experiencing a bleeding episode that requires factor replacement treatment between the screening

visit and the subsequent visit, the subject will be treated with rVWF (vonicog alfa). If rVWF (vonicog alfa) is not available for any reason, (e.g., study site visit for IP administration not feasible, IP not available due to extraordinary circumstances such as COVID-19, etc.) the subject may use standard of care, such as commercial pdVWF/FVIII products, and the reason for the use of non-IP products should be clearly documented.

For newly enrolled subjects in Cohort 4, in the event of a subject experiencing a bleeding episode that requires factor replacement treatment between the screening visit and the subsequent visit (ie, initial PK assessment/baseline visit), the subject will be treated with 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.

8.3.2 Pharmacokinetic Assessment - Initial PK (Cohort 4 only)

Subjects in Cohort 4 will complete the initial PK assessment as shown in Table 3 and Table 7. After screening and confirmation of eligibility, subjects will undergo a PK assessment. PK assessment is to be performed following a washout period of at least 5 days. The subject should not be actively bleeding at the time of PK assessment. Subjects will receive a dose of 50 (±5) IU/kg rVWF:RCo to determine VWF and FVIII activities. 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 (can be performed at 10 [±1] hours for the subject's convenience), 24 [±0.5] hours, 30 [±2] hours, 48 [±2] hours, 72 [±2] hours, and 96 [±2] hours). 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 that requires treatment between the screening and the PK infusion with the IP for Initial PK assessment visit and the subject is treated with his/her standard of care, such as commercial pdVWF/FVIII products, a washout period of at least 5 days is required prior to rVWF (vonicog alfa) PK infusion at the PK assessment visit. If a subject experiences a bleeding episode requiring treatment during the PK assessment, rVWF (vonicog

alfa) should be used to treat the bleed and no subsequent blood sample will be drawn in that specific PK period. The guidance provided in Section 6.2.2 has to be followed for the treatment of the bleeding episode. Once recovered, the subject is eligible to repeat the PK assessment.

8.3.3 Prophylaxis Initiation Visit (Cohort 1, Cohort 2, Cohort 3, and Cohort 4)

The prophylaxis initiation visit will occur within 42 days after screening and upon confirmation of eligibility. For subjects transitioning from Study 071301 and 071102 to Cohorts 1, 2 and 3 in this study, the prophylaxis initiation visit is expected to be on the same day of screening visit unless approved by the Sponsor under special circumstances (eg, COVID-19). For new subjects in Cohort 4, 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-hr post-infusion PK assessment, the subject receives the first IP infusion for prophylactic treatment (prophylaxis initiation visit). The 96-hr post-infusion PK sampling should be conducted on the same day along with the drawing of prophylaxis pre-infusion sample (Table 7). Details on dose are provided in Section 6.2.2.1.

8.3.4 Follow-Up Study 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 3 months (±2) weeks for subjects in Cohort 1, Cohort 2, Cohort 3, and Cohort 4. Follow-up (FU) study visits for subjects in OD treatment arm (Cohort 5 and Cohort 6) will be performed at every 3 months (±2) weeks after screening. Additional visits may occur if clinically indicated (see Section 8.3.5). When possible, site visits should be scheduled on days when the subjects in Cohorts 1-4 are expected to infuse planned prophylactic rVWF (vonicog alfa). Within 2 hours prior to the prophylactic 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. IR will be determined at each FU visit (until the 12-month visit) based on VWF:RCo activity assessed prior to and after IP infusion. Immunogenicity will be assessed quarterly throughout the study at the scheduled FU visits, or, during unscheduled visits, if sampling for immunogenicity assessment cannot be performed during scheduled visits due to special circumstances.

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 OD subjects, a washout period of at

least 72 hours after the last infusion applies before the blood draw for the immunogenicity assays. For subjects receiving regular prophylactic treatment in Cohorts 1-4, if an IP infusion is administered (for any reason, including treatment of a breakthrough bleed or a delayed planned prophylactic infusion) after the last scheduled prophylactic infusion and before the scheduled FU visit during which the next scheduled prophylactic infusion would be expected to be administered, the FU visit should be rescheduled for proper pre-infusion sampling to be performed for assessment of neutralizing and binding antibodies, clinical chemistry and hematology.

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 weeks and 12 months ± 2 weeks visits an electrocardiogram (ECG) will be performed and PRO 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.

8.3.5 Unscheduled Visit

For any unscheduled visit (except for collection of IP) a clinical assessment will be performed as per the scheduled follow-up visits except for HRQoL, ECG, and IR determination unless the unscheduled visit serves as a replacement for any missed scheduled FU visit (missed FU visit would still be a protocol deviation but should be captured along with the reason for not having performed the scheduled FU visit). Subjects who have >1 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.

8.3.6 End of Study Visit/Termination Visit

Subjects will participate in this study for at least 12 months. After this 12-month period, the end of study visit is scheduled once rVWF (vonicog alfa) is commercially available in their respective countries or until subjects have been treated in the study for a maximum of 3 years, whichever occurs earlier. Any subject who discontinues the study treatment should have a termination visit as soon as possible after the decision to discontinue trial treatment. If a subject's

decision to discontinue the study participation occurs prior to rVWF (vonicog alfa) is commercially available in their respective country or until the subject has been treated in the study for a maximum of 3 years but after the subject has completed at least 12 months on study treatment, then the subject will be considered as "completed study treatment". A washout period of at least 72 hours is required between the last infusion and the EOS/ termination visit. The EOS/termination visit will comprise a full assessment for safety and immunogenicity.

Additionally, Subjects in Cohorts 1, 2, 3, and 4 will undergo a PK/PD assessment at the End of Study Visit using their last scheduled prophylactic dose. The EOS PK assessment IP infusion should occur 96 hours after the preceding infusion and will be given at the study site after the blood sample for immunology testing is drawn. Blood samples for PK/PD analysis 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 this PK assessment, no subsequent blood sample will be drawn. The subject, once recovered, is eligible to repeat the PK assessment.

8.3.7 Follow-up Period

Not applicable.

8.3.8 Additional Care of Subjects after the Study

No aftercare is planned for this study.

8.3.9 Subject Diary

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
- Details of bleeding episodes (site, type, severity and date/time of bleeding) and response to treatment as described in Section 8.4.2.4
- Subjective (subject's) hemostatic efficacy assessments
- Untoward events/unwanted experiences
- Concomitant medications (including immunizations) and non-drug therapies
- 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 subject 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.

E-diary use is not optional; it is required per protocol. Therefore, if the subject or caregiver experiences any problem with the use of the e-diary, they should inform the site/Investigator immediately and follow the instructions given to record any information on the use of IP (including the regular planned prophylactic infusions and infusions to treat any acute bleed), on the bleeds experienced, untoward events, concomitant medications, and health resource use, until these data can be recorded in a properly working e-diary.

8.4 Study Assessments

8.4.1 Demographic and Other Baseline Characteristics

Subject demographic information and Other Baseline Characteristics including gender, age, and race, medical history, prior medications, latest bleeding episodes, OD treatment, investigator assessment of hemostatic efficacy, etc. will be collected prior to the subject receiving the first dose of IP.

8.4.2 Efficacy

8.4.2.1 Assessment of Spontaneous Bleeding Episodes/ABR

The 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), by 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 13)
- 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
- Type and number of analgesics as well as additional hemostatic treatments required
- Other concomitant medications
- Non-drug therapies
- AEs (refer to Appendix 3.1)

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 by the investigator. Bleeding occurring at multiple locations related to the same injury (e.g., knee and ankle bleeds following a fall) should be counted as a single bleeding episode by the investigator.

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 but should be reported to the medical monitors and the study team. The use of non-IP product and the reason should be documented.

8.4.2.2 Evaluation of Spontaneous 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 OD treatment. The ABR during the 12 months before prophylactic treatment will be the baseline for evaluation of ABR under rVWF prophylactic treatment (Cohort 4). The maximum interval of bleed-free periods as well as trauma induced bleeding episodes will also be recorded.

8.4.2.3 Number of Infusions and Total Weight-adjusted Consumption of rVWF and ADVATE

The number of rVWF (vonicog alfa) and, if/when needed, 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.

8.4.2.4 Assessment of Efficacy for Treatment of Bleeding Episode

Investigators will be asked to assess and record hemostatic efficacy after resolution of each bleeding episode, as soon as possible, preferably within 24 hours after the bleed resolution, using the 4-scale rating system outlined in Table 14. In order to perform the hemostatic efficacy assessment for any acute bleeding episode, the investigator should be contacted by the subject/subject's care giver as soon as a bleeding episode is experienced by the subject. Once contacted by the subject/care-giver, the investigator should collect the information on the nature eg, spontaneous or traumatic), location (eg, oral/gum, nose/epistaxis, etc), and severity (eg, severe, moderate, mild/minor) of the bleed to be able to provide the subject with the instruction on how to treat the bleed (eg, how many infusions of IP may be needed to stop the bleeding). Investigator's estimate on the number of IP infusions needed to treat the bleeding episode will be used by the investigator to compare it to the number of actual infusions that were given to the subject to stop the bleed to be able to assess the hemostatic efficacy per 4-point Efficacy Rating Scale (Table 14).

Table 14. 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

Table 14. Efficacy Rating Scale

Rating	Efficacy Rating Criterion	
	Minor and Moderate Bleeding Events	Major Bleeding Events

* e.g., If estimated number of infusions is 1, then 2 actual infusions sufficient to stop the bleeding will be considered "Good". If estimated number of infusions is 2, then 3 actual infusions will be considered "Good". If estimated number of infusions is 2, then 1 actual infusion will be considered "Excellent".

8.4.2.5 Assessment of Efficacy for Treatment for Surgical Bleeding

For those undergoing surgery, the operating surgeon will be asked to assess and record actual versus predicted 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 15.

Table 15. 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

8.4.3 Safety

8.4.3.1 Adverse Events

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (e.g., "Have you had any health problems since your last visit?"). AEs are collected from the time informed consent is signed. See Appendix 3 for AE definitions, assessment, collection time frame, and reporting procedures.

8.4.3.2 Thromboembolic Events

Thromboembolic events are considered important identified 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 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 Data Monitoring Committee, if applicable.

8.4.3.3 Hypersensitivity Reaction

Anaphylactic reaction 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], and hypoxemia)
    b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, and 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 (Appendix 3). Additional blood draws for Anti-VWF immunoglobulin E (IgE) antibody testing will be drawn.

8.4.3.4 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.

8.4.3.5 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Appendix 3). 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 Serious Adverse

Event Report (SAER). These events will not be considered as SAEs and will not be included in the analysis of SAEs.

8.4.3.6 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.

8.4.3.7 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary. The subject's medical history will also include documented history of OD 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 30 days prior to study entry and all concomitant medications and non-drug therapies during study will be recorded on the CRFs. COVID-19 vaccination information will be recorded as prior or concomitant medication.

Data on medical history, drug and non-drug therapy history of subjects transitioning from study 071301 or 071102 will be used from the eCRF of the prior studies, will be updated, if applicable, and transcribed into the respective eCRF of this study.

8.4.3.8 Physical Examination

At screening and subsequent study visits, a physical examination will be performed by the investigator. A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of the general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological.

Abnormalities identified at the screening visit and at subsequent study visits will be recorded in the subject's source documents. 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 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.

8.4.3.9 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)
- Systolic/diastolic blood pressure (mmHg) baseline measurements will be measured after a 10-minute rest in the supine/semi-recumbent position.
- Pulse (beats/min) will be measured at the distal radial arteries under the same conditions as above.
- Respiratory rate (breaths/min) will be measured over a period of 1 minute under the same conditions as above.
- Body temperature (ºC or ºF) 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 will be measured at screening and within 30 minutes before and 30 ± 15 minutes after administration of IP, at each study visit, and at study completion/termination. Blood pressure will be measured when subjects are in the supine/semirecumbent position.

The investigator will assess whether a change from baseline (screening visit) in vital signs may be deemed clinically significant and whether the change should be considered and recorded as an AE. 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 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.

8.4.3.10 Electrocardiogram

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

8.4.3.11 Clinical Laboratory Tests

All clinical laboratory tests will be performed according to the laboratory's standard procedures. Reference ranges will be supplied by the laboratory and used to assess the results for clinical significance and out-of-range changes which may be associated with, or constitute, an AE. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

A complete list of the clinical laboratory tests to be performed is provided in Appendix 2.

8.4.3.11.1 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 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, 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. In

general, all laboratory tests will be performed at central laboratories, except the pregnancy and blood group tests which will be performed at the local laboratory. In some cases, i.e. under extraordinary circumstances including any condition that may be considered of medical urgency per investigator's assessment or limitations due to public health safety measures, local laboratory can be used (e.g. to ensure the immediate availability of the result) after discussion with medical monitor and explicit approval by sponsor/CRO, and a back-up sample should be drawn for confirmatory measurement at the central laboratory. In principle, results from the central laboratory will be used for data analysis purposes. 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, hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), or parvovirus B19 (B19V) shall be re-tested.

8.4.3.12 Pregnancy Test

A urine and/or serum beta-hCG pregnancy test will be performed on all females of child-bearing potential at the screening visit and, if deemed necessary by PI, can be ongoing basis at any time during the study, if pregnancy is suspected; or on withdrawal of the subject from the study.

8.4.3.13 Immunology

8.4.3.13.1 Antibodies to VWF and FVIII

All subjects will be tested for binding and neutralizing antibodies to VWF and FVIII at each of the scheduled visits. 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.

The assays to detect neutralizing and total binding anti-VWF antibodies have been validated. 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. These subjects need to be closely monitored and therapy adjusted accordingly.

8.4.3.13.1.1 Neutralizing Antibodies to VWF

Three functional VWF assays, VWF:CB, 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 the Bethesda assay with Nijmegen modification (Kasper 1991). 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.

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 (CI) of the underlying assays, making determinations at the end of the evaluation range of the Bethesda reference curve uncertain (Lillicrap 2008).

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

8.4.3.13.1.2 Binding Antibodies to VWF

The presence of total binding anti-VWF antibodies will be determined by an enzyme-linked immunosorbent assay (ELISA). 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).

Plasma samples are analyzed for binding antibodies against the specific antigen in 2 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. 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 2 independent duplicates. The cut off level is established based on background signal level of healthy plasma donors (n>100) 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.

8.4.3.13.1.3 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 confirmed by a second test performed on an independent sample obtained 2 to 4 weeks following the first test. Only confirmed positive FVIII inhibitor test result will be reported as an SAE.

8.4.3.13.1.4 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.

8.4.3.13.2 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. Antibodies to the other proteins will be tested at Screening, every 6 months during follow-up, and at the End of Study visit. Antibody containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

8.4.3.13.2.1 Anti-CHO Protein

Total Ig antibodies 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).

8.4.3.13.2.2 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 (human anti- mouse antibodies [HAMA]). 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).

8.4.3.13.2.3 Antibodies to Human Furin

Total Ig antibodies 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).

8.4.4 Pharmacokinetics and Pharmacodynamics

For subjects in Cohort 4, a PK/PD 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.

Subjects in Cohorts 1, 2, 3, and 4 will undergo a PK/PD assessment at the End of Study Visit using a scheduled dose. The PK assessment IP infusion should occur 96 hours after the preceding infusion and will be given at the study site after the blood sample for immunology testing is drawn.

At both the initial and EOS PK/PD assessment, blood samples will be drawn within 30 minutes pre-infusion, and at 11 time points postinfusion (15 [±5] minutes, 30 [±5] minutes, 60 [±5] minutes, 3 [±0.5] hours, 6 [±0.5] hours, 12 [±0.5] hours (may be drawn at 10 [±1] hours for subject convenience), 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. FVIII activity will be measured using the 1-stage clotting assay to assess the PD of rVWF (vonicog alfa).

If a subject experiences a bleeding episode during the PK/PD assessment, no subsequent blood sample will be drawn in that specific PK/PD period. The guidance provided in Section 6.2.2 has

to be followed for the treatment of the bleeding episode. The subject, once recovered, is eligible to repeat the PK/PD assessment.

IR will be determined at each follow-up visit (until the 12-month visit) based on VWF:RCo activity assessed prior to and after IP infusion. rVWF (vonicog alfa) will be infused at the regular prophylactic dose. The blood sample for IR analysis will be drawn within 30 minutes prior to IP infusion and 30 minutes ±5 minutes after IP infusion.

8.4.5 Health-related Quality of Life (HRQoL), Treatment Satisfaction and Healthcare Resource Utilization

8.4.5.1 HRQoL

Health related Quality of Life assessment for the subjects ≥18 years of age, is based on 3 questionnaires: EuroQoL 5-dimension questionnaire 3 level version (EQ-5D-3L) (Rabin and de Charro 2001), Short Form (36) Health Survey (SF-36) (Ware and Sherbourne 1992), and Von Willebrand Impact Questionnaire (V-WIQ) (Ito et al. 2011). Assessment for pediatric subjects between 2 and 18 years of age at screening, is based on 3 questionnaires: EQ-5D-Y (for subjects aged ≥7 years, parent-proxy version for ages 4 to <7 years) (Rabin and de Charro 2001) and PedsQL™ (Varni et al. 1999), Visual Analog Scale (VAS) Pain Score. Pediatric subjects aged <2 years will not complete HRQoL questionnaires.

A named member of study site staff will administer these questionnaires to all subjects at the following time points:

- Screening visit/baseline (PK assessment) visit
- Study follow-up visit (after 6 months [±2] weeks)
- Study Completion Visit (after 12 months [±2] weeks)

The SF-36 is a validated, generic HRQoL instrument, measuring physical, emotional, social functioning as well as overall general health. It captures the following 8 domains: Role Physical, Bodily Pain, Physical Functioning, General Health, Vitality, Social Functioning, Role Emotional and Mental Health.

The V-WIQ questionnaire is a newly developed, disease-specific instrument that assesses the physical, emotional well-being of adult individuals with VWD.

The generic PedsQL™ is a 23-item questionnaire for subjects 13 to 17 years of age that assesses physical functioning (8 items); emotional functioning (5 items); social functioning (5 items); and school functioning (5 items). For younger children, there are parent-proxy versions for the age

groups of 2 to 4 years (21 items) and 5 to 7 years (23 items) and a child version for the age group of 8 to 12 years (23 items).

The EuroQoL 5-dimension questionnaire 3 level, EQ-5D-3L, is a tool to assess health status in subjects ≥18 years of age that has 5 socially relevant domains: mobility, self-care, usual activity, pain-discomfort, and anxiety-depression. The subject uses a visual analog scale to provide a self-assessment of their health, ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). For children 7 to 17 years, there is a child version, EQ-5D-Y, and a parent-proxy version is used for children 4 to <7 years of age.

A VAS Pain scale will be used for subjects to rate their level of pain.

8.4.5.2 Treatment Satisfaction

Treatment Satisfaction will be assessed using The Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) (Bharmal et al. 2009), which is a validated measure used to assess treatment satisfaction with medication in patients. It is comprised of 9 questions that provide scores on 3 scales: Effectiveness (3 items), Convenience (3 items), Global Satisfaction (3 items).

Three sub-scales domain scores range from 0 to 100 with higher scores representing higher satisfaction with the treatment on that domain.

8.4.5.3 Healthcare Resource Utilization

The subject's use of health resources such as hospitalizations, emergency room visits, and doctor's office visits will be recorded. The impact of VWD on the subject's health will also be assessed through recording the number of days missed from school or work.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

Any protocol deviations surrounding COVID-19 or other public health emergencies will be clearly identified, described, and documented in a systematic way and in line with regulatory authorities' recommendations. These protocol deviations will be summarized separately in the clinical study report. These data may be handled differently in the final data analysis, with documentation in the SAP.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock, or earlier if required by applicable standard operating procedures.

All statistical analyses will be performed using SASÒ (SAS Institute, Cary, NC 27513) version 9.4 or later.

9.2 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

An interim analysis will be performed after all subjects in prophylactic treatment cohorts have completed the 12-month visit. Additional interim analyses may be performed as needed to support submissions to health authorities. The interim analysis will be performed on a cleaned snapshot of the study database. The interim analysis data will be used in preparing an interim clinical study report and in support of regulatory submissions.

A DMC will be involved in the management of this study. The purpose of the DMC is to ensure the safety of the subjects in the study by reviewing the study data on an ad hoc basis. Further details regarding the DMC can be found in the DMC charter, which will be available prior to the administration of investigational product.

9.3 Sample Size and Power Considerations

Up to 71 pediatric/adolescent and adult subjects with severe VWD (including at least 5 newly enrolled subjects with type 3 VWD on prophylaxis regimen) will be included, composed of a) up

to 22 adult subjects transitioning from study 071301; b) up to 34 pediatric/adolescent subjects transitioning from Study 071102; c) at least 7 and up to 15 newly enrolled adult and pediatric/adolescent (aged 12 to <18 years) subjects who have been receiving VWF products for OD treatment.

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

9.4 Statistical Analysis Set(s)

- The safety analysis set will be composed of all subjects who received any amount of rVWF (vonicog alfa).
- The full analysis set (FAS) will be composed of all enrolled subjects who received IP treatment.
- The PK analysis set (PKAS) will be composed of all subjects who completed the required washout period, received the study drug infusion, and have at least 1 quantifiable post-dose measurement without any significant protocol deviations or events with potential to affect PK.
- The per protocol analysis set (PPAS) will be composed of all subjects in the FAS who have no major deviations from the protocol affecting the efficacy study results. Major protocol deviations will be defined in the Protocol Deviation Plan.

9.5 Efficacy Analyses

9.5.1 Primary Efficacy Endpoint

The primary outcome measure, spontaneous ABR during the first 12 months on prophylactic treatment with rVWF (vonicog alpha), will be calculated as the number of spontaneous (as assessed by the investigator) bleeds requiring treatment with a VWF product during the first 12 months on study treatment, and summarized through descriptive statistics by prophylactic cohort (Cohorts 1 to 4), and age group. The primary analysis will be based on the FAS and will be repeated on the PPAS as sensitivity analysis.

9.5.2 Secondary Efficacy Endpoints

All secondary efficacy endpoints will be analyzed on the FAS by age group and cohort on 12-month data and the entire study. Continuous endpoints will be summarized by mean (2-sided 95% CI when appropriate), standard deviation, median, range and quartiles. Categorical

endpoints will be summarized by proportions and 2-sided 95% CI will be provided when appropriate.

9.5.2.1 Efficacy of Prophylaxis

The spontaneous ABR (as calculated for the primary endpoint) will be summarized through descriptive statistics by prophylactic cohort (Cohorts 1 to 4) and age group.

For Cohorts 1 to 4, the number and proportion of subjects with dosing frequency of 1, 2, and ≥3 weekly will be evaluated at the end of completion of the 12-month treatment period and at the end of the study, in total and by cohort and age group, accompanied by a 2-sided 95% CI.

The number and proportion of subjects with categorized spontaneous ABR (i.e., 0, 1 to 2, 3 to 5, or >5 bleeds) will be provided by cohort and age group, accompanied by a 2-sided 95% CI.

Summary statistics for the time to first bleeding event will be provided by cohort and age group using Kaplan-Meier plots.

The spontaneous ABR (as calculated for the primary endpoint) will also be summarized by location of bleeding (GI, epistaxis, joint bleeding, menorrhagia, oral, muscle and soft tissue, etc.).

Summary statistics for the total number of infusions, average number of infusions per week, as well as number (proportion) of subjects on different prophylaxis dosing regimens will be provided by cohort and age group. The total weight-adjusted consumption of rVWF (vonicog alfa) (and of ADVATE [rFVIII, octocog alfa] if applicable) during prophylactic treatment will be provided similarly.

The count and proportion of subjects that require no transfusion over time to maintain hemoglobin level will be calculated and summarized by cohort and age group. The ferritin levels over time will be summarized descriptively.

9.5.2.2 Efficacy of Treatment of Bleeding Episodes

The efficacy rating will be followed for the first 12 months (on study treatment) only.

For the number of infusions of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) per bleeding episode, for the weight-adjusted consumption of rVWF (vonicog alfa) and ADVATE (rFVIII, octocog alfa) per bleeding event as well as for the overall hemostatic efficacy rating at resolution of bleed, summary statistics will be presented.

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

9.5.3 Multiplicity Adjustment

Not applicable.

9.5.4 Control of Type I Error

Not applicable.

9.5.5 Exploratory Endpoints

9.5.5.1 Efficacy of Perioperative Management

The analysis will be performed on the FAS for the first 12 months of study data, except for the weight-adjusted dose that will be followed for the entire study.

Descriptive statistics will be performed for the following outcome measures:

- Intraoperative actual versus predicted blood loss (assessed by operating surgeon) at completion of surgery.
- Intraoperative hemostatic efficacy score on a scale of excellent, good, moderate or none (assessed by operating surgeon) at completion of surgery.
- Overall hemostatic efficacy by the investigator 24 hours after the last perioperative infusion of rVWF (vonicog alfa) or at day 14 post operation, whichever occurs first.
- Daily intra- and postoperative weight-adjusted dose of rVWF (vonicog alfa) with or without ADVATE (rFVIII, octocog alfa) through postoperative Day 14.

9.6 Safety Analyses

Safety analysis will be performed on the safety analysis set by age group overall and by cohort on 12, 24-month data and the entire study data.

Treatment-emergent AEs (TEAEs) are defined as AEs with start dates on or after the first exposure to IP. Summaries on AEs will be based on TEAEs unless otherwise indicated.

Frequency counts and percentages will be calculated for AEs and SAEs and presented in summary tables. AEs will be cross-tabulated for relatedness, seriousness, and severity. AEs will be categorized according to MedDRA dictionary and summarized by system organ class (SOC) and preferred term. Counts, frequency and annualized rates for thrombotic events and

hypersensitivity reactions together with exact Clopper-Pearson 2-sided 95% CI on their occurrence will be tabulated.

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. Causally related AEs 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.

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 IgG and rFurin.

Vital signs and laboratory parameters will be summarized descriptively. Shift tables will be prepared for laboratory parameters. Clinically significant abnormal values in routine laboratory parameters and vital signs will be summarized.

9.7 Other Analyses

9.7.1 Pharmacokinetic/Pharmacodynamic Analyses

A listing of PK blood sample collection times as well as derived sampling time deviations for VWF:RCo, VWF:Ag, VWF:CB, and FVIII activity will be provided.

PK and PD parameters will be derived using noncompartmental methods with Phoenix® WinNonlin® Version 6.4 or higher (Certara, L.P. Princeton, New Jersey, US) and/or SAS® Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, US).

All PK and PD analyses will be based on the PKAS and will use actual elapsed time from the start of infusion, rather than scheduled sampling times, wherever possible. 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 excluded 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. Subjects with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for meaningful analysis.

The following PK parameters, based on the serial PK assessment, will be calculated for each adult subject and for each pediatric subject when applicable in Cohort 1, 2, 3, or 4 and reported using descriptive statistics for VWF:RCo, VWF:Ag, and VWF:CB: incremental recovery (IR), half-live ($T_{1/2}$), mean residence time (MRT), area under the plasma concentration /time curve from time 0 to infinity ($AUC_{0-\infty}$), area under the plasma concentration/time curve from time 0 to 96 hours postinfusion/dose (AUC_{0-96h}), maximum concentration (C_{max}), time to maximum concentration (T_{max}), apparent steady-state volume of distribution (V_{ss}), and clearance (CL). The corresponding PD of rVWF (vonicog alfa) as measured in FVIII activity by the 1-stage clotting assay (FVIII:C) will be assessed using C_{max}, T_{max}, and AUC_{0-96h}.

Details of calculation of PK and PD parameters and corresponding analysis will be provided in the statistical analysis plan.

Pharmacokinetic and PD variables (concentration/activity and parameters) will be listed and summarized using appropriate descriptive statistics.

Incremental recovery will be summarized by visit and displayed graphically over time for each subject of prophylactic cohorts (Cohorts 1 to 4) for the initial 12 months of prophylactic treatment.

9.7.2 Health-related Quality of Life, Treatment Satisfaction and Health Resource Use Data Analyses

The analysis will be performed on the FAS by cohort and age group at baseline, 6, and 12 months, and at the end of the study.

The HRQoL, TSQM-9 and health resource use data will be summarized descriptively and listed per subject. For all calculated scores of each questionnaire, descriptive statistics will be calculated by visit by age group and by cohort.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

APPENDIX 1. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Appendix 1.1 - Regulatory and Ethical Considerations

This study is conducted in accordance with current applicable regulations including ICH E6, EU Directive 2001/20/EC, and all updates, as well as local ethical and legal requirements.

Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

The name and address of each third party vendor (e.g., CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

Appendix 1.2 - Sponsor's Responsibilities

Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, current International Council for Harmonisation Good Clinical Practice (ICH GCP) Guidelines, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

In the event of public health emergencies such as the COVID-19 pandemic, alternative approaches may be used to ensure data quality and integrity as well as maintaining subject safety (eg, remote source data verification [SDV]).

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the CRO/investigator as necessary.

Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

The timing for study registration and results summary posting must be in accordance with applicable local and national requirements.

Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance. The sponsor will provide the ECs with a copy of the same summary.

Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and institutional review boards (IRBs)/ethics committees (ECs) are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

The sponsor will make an end of study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

Appendix 1.3 - Investigator's Responsibilities

Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP E6 R2 (2016), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

Protocol Adherence and Investigator Agreement

The investigator and any sub-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for

multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

Documentation and Retention of Records

Case Report Forms

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

The CRA/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, original clinical laboratory reports, and histology and pathology reports.

All key data must be recorded in the subject's source documents.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (e.g., subject's medical file, appointment books, original laboratory reports, X-rays etc.).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (e.g., the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

Appendix 1.4 - Data Management Considerations

Data Collection

The investigators' authorized site personnel must enter the information required by the study CRF Completion Guidelines or similar for all data requiring transcription of the source. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. In the event of public health emergencies such as the COVID-19 pandemic, the study monitor may be permitted to review the CRF data against the source data remotely where allowed by local laws and regulations.

Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting.

Data Management

Data are to be entered into a clinical database as specified in the CRO's data management plan or similar. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

Data Handling

Not applicable to this study

Appendix 1.5 - Ethical Considerations

Informed Consent

It is the responsibility of the investigator to obtain written informed consent and assent from all study subjects prior to any study-related procedures including screening assessments. All consent and assent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent and assent documentation (i.e., a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

In the event of public health emergencies such as the COVID-19 pandemic, the subject and/or other signatories required by local regulations may provide informed consent by alternative methods (eg, telephone, fax, eConsent) per the investigator's local and/or central IRB or IEC guidance.

Within the source documents, site personnel should document instruction of and understanding by the parent/legally authorized representative/caregiver of the safe, responsible storage and administration of investigational product to the study subject.

The principal investigator provides the sponsor with a copy of the consent form and assent form where applicable that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start

that another party (i.e., sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement. Investigational product supplies will not be released until the CRO has received written IRB/EC approval.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol at least annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. This can be the responsibility of the sponsor or investigator for sites within the EU; or for multicenter studies, the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs as required by IRB/EC procedures.

Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the HIPAA of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the CRO.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market rVWF; national or local regulatory authorities; and the IRBs/ECs which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities. Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected, if permitted under local laws governing privacy.

The results of studies containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth, where allowed per local law, may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

Study Results/Publication Policy

The term "Publication" shall mean any paper, article, manuscript, report, poster, internet posting, presentation slides, abstract, outline, video, instructional material, presentation (in the form of a written summary), or other public disclosure of the study results, in printed, electronic, oral, or other form. The parties understand and agree that participation in the study may involve a commitment to publish the data from all sites participating in the study in a cooperative publication with other investigators prior to publication or oral presentations of the study results on an individual basis. The site agrees not to publish or present the site's study results until such time as either the aggregate multi-site study results are published in a cooperative publication or for a period of 1 year after termination or completion of the study at all participating sites, whichever shall first occur. After that time, the site may publish the site's study results in scientific journals or present the study results at symposia or other professional meetings in accordance with the following provisions:

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results

from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single site data being presented.

At least sixty (60) days prior to submitting an abstract, manuscript, or other document for publication, a copy of the proposed publication will be provided to the sponsor by the site for review. Upon the sponsor's request, the site agrees to remove any and all confidential information (expressly excluding study results) identified in the publication and to delay such submission or presentation for an additional sixty (60) day period in order to allow the sponsor time to file any patent application(s). All publications of the study results shall appropriately reference the multi-site study publication, if any, or the fact that the study results are a subset of data resulting from a larger multi-site study.

The sponsor is committed to transparent dissemination of all scientific, technical and medical manuscripts generated from sponsor-supported research. Therefore, after January 1, 2018, the sponsor will require the submission of all sponsor-supported research manuscripts to journals that offer public availability via Open Access (including publisher platforms/repositories and self-archiving). Open Access refers to the free at point of entry, online availability of published research output with, where available, rights of re-use according to an End User License.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) Recommendation for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical journals. Participation as an investigator does not confer any rights to authorship of publications.

APPENDIX 2. CLINICAL LABORATORY TESTS

The following clinical laboratory assessments will be performed:

Chemistry	Creatinine Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Bilirubin Albumin Total bilirubin (TBL) Total protein Blood Urea Nitrogen Glucose Sodium Potassium Chloride Bicarbonate
Hematology	Erythrocytes (Red Blood Cell [RBC]) Leukocytes (White Blood Cell [WBC]) Hemoglobin Hematocrit Mean corpuscular volume [MCV] Mean corpuscular hemoglobin [MCH] Mean corpuscular hemoglobin concentration [MCHC] WBC Differential count (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils) Platelet Ferritin (Fe)
Urinalysis	Specific gravity Urobilinogen Ketones pH Protein Bilirubin Nitrite Glucose

	Erythrocytes
Coagulation Panel/ PK assessment	Prothrombin time (PT) International normalized ratio (INR)/activated partial thromboplastin time (aPTT) Von Willebrand factor: Ristocetin cofactor (VWF:RCo) Von Willebrand factor antigen (VWF:Ag) Von Willebrand factor collagen binding activity (VWF:CB) Factor VIII clotting activity (FVIII:C)
Immunogenicity assessment	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 may 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.
Viral Serology	Hepatitis A Antibody, Total; Hepatitis A Antibody, IgM; Hepatitis B Surface Antibody; Hepatitis B Core Antibody, Total; Hepatitis B Core Antibody, IgM; Hepatitis B Surface Antigen; Hepatitis C Virus Antibody; Parvovirus B19; Human Immunodeficiency Virus (HIV-1/HIV-2) Antibodies
Pregnancy Test	Serum or Urine human chorionic gonadotropin (hCG)[1]

VWD gene mutational analysis, VWF multimer analysis and blood group analysis will be determined at screening if the information is not already available in the subject's medical history.

Additional Laboratory Testing in Case of Thromboembolic Events: VWF Multimer Analysis, ADAMTS13 Activity, Soluble P-Selectin (sP-Selectin), D-Dimer,

Additional Laboratory Testing in Case of Severe Hypersensitivity Reactions: anti-VWF IgE antibody

1. Only women with childbearing potential (excluding menopausal women or women with surgical contraception) will receive the serum or urine hCG test at Screening Period and, if necessary, during the study.

In the case of a public health emergency, such as the COVID-19 pandemic, serum samples should continue to be sent to the designated central lab according to protocol when possible (e.g. when courier service is available). The Sponsor and CRO will work with courier companies to identify and implement an alternative courier, route, or system where possible.

APPENDIX 3. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Appendix 3.1 - Adverse Event Definitions

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this investigational product or medicinal product. An AE can therefore be any unfavorable and unintended sign (including a clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not causality is suspected (ICH Guidance ERA 1995).

Treatment-emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as any event emerging or manifesting at or after the initiation of treatment with an investigational product or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the investigational product or medicinal product.

Serious Adverse Event

A serious adverse event (SAE) is any untoward clinical manifestation of signs, symptoms or outcomes (whether considered related to investigational product or not and at any dose:

- Results in death
- Is life-threatening. Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of hospitalization. Note: Hospitalizations that are the result of elective or previously scheduled investigations procedures or surgery for pre-existing conditions and have not worsened after initiation of treatment should not be classified as SAEs.
- For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Results in a congenital abnormality/birth defect

- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include:
- Bronchospasm associated with anaphylaxis requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.
- Reviewed and confirmed seroconversion for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), or parvovirus B19 (B19V)

For this protocol, the following events will not be collected as SAE(s):

- 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.

Unexpected Adverse Event

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 (RSI). “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 product, but are not specifically mentioned as occurring with the particular product under investigation.

The expectedness of AEs will be determined by the sponsor using the IB as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated form the pharmacological properties of a product.

Suspected Unexpected Serious Adverse Reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as 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

Symptoms of the Disease under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected disease progression and are part of the efficacy or effectiveness data collected in the study. Significant worsening of symptoms should be recorded as an AE.

Preexisting conditions prior to randomization or initiation of study medication are described in the medical history, and those that manifest with the same severity, frequency, or duration after drug exposure, are not be recorded as AEs. However, when there is an increase in the severity, duration or frequency of a preexisting condition, the event must be described on the AE CRF.

Clinical Laboratory and Other Safety Assessment

A change in the value of a clinical laboratory parameter, vital sign measure, or ECG assessment can represent an AE if the change is clinically relevant or if, during administration of investigational product, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further waning of an already clinically significant value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration with the investigational product, and the range of variation of the respective parameter within its reference range, should also be considered.

If, at the end of the treatment phase, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), vital sign, or ECG values which were not present at the pretreatment evaluation observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible

explanation (e.g., concomitant disease or expected disease evolution) is found for the abnormal values.

The investigator should assess, based on the above criteria and the clinical condition of the subject, whether a change in a clinical laboratory value, vital sign, or ECG parameter is clinically significant and represents an AE.

Collection of ECG parameters is suggested to be performed in triplicates and conducted by a central laboratory for all study subjects.

Appendix 3.2 - Collection of Adverse Events

All AEs/SAEs are collected from the time the informed consent document is signed until the defined follow-up period stated in Section 8.3.7. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered.

All AEs/SAEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to baseline), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained.

Appendix 3.3 - Assessment of Adverse Events

Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity is captured as a new event. Worsening medical conditions, signs or symptoms present prior to initiation of investigational product, must be recorded as new AEs.

For example, if a subject reports mild intermittent dyspepsia prior to initiation of dosing with the investigational product, and the dyspepsia becomes severe and more frequent after first dose a new AE of severe dyspepsia (with the appropriate date of onset) should be documented in the source.

The medical assessment of severity is determined by using the following definitions:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

- Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source.

The following additional guidance may be helpful:

Table A1 Adverse Event Relationship Categorization

Related	The temporal relationship between the event and the administration of the investigational product is compelling enough and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

Outcome Categorization

The outcome of AEs must be documented in the source during the course of the study. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

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.

COVID-19 Vaccination-related AE

If applicable, AE will be assessed by the Investigator whether it is related to COVID-19 vaccination and the assessment will be recorded on the AE CRF.

Appendix 3.4 - Safety Reporting

Reference Safety Information

The RSI for this study is included in the IB which the sponsor has provided under separate cover to all investigators.

Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Takeda Global Patient Safety Evaluation (GPSE) Department and the CRO/Takeda medical monitor within 24 hours of becoming aware of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Appendix 3.9) unless they result in an SAE.

The investigator must complete, sign, and date the Takeda "Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol", verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested), and fax or e-mail the form to the Takeda GPSE. A copy of the Takeda "Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol" (and any applicable follow-up reports) must also be sent to the CRO/Takeda medical monitor using the details specified in the emergency contact information section of the protocol.

Appendix 3.5 - Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to investigational product) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 8.3.7 and must be reported to Takeda GPSE Department and the CRO/Takeda medical monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to Takeda GPSE Department within 24 hours of the reported first becoming aware of the event.

Appendix 3.6 - Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms reported by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

Appendix 3.7 - Fatal Outcome

Any SAE that results in the subject's death (e.g., the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (e.g., drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of withdrawn should not be selected solely as a result of the subject's death.

Appendix 3.8 - Pregnancy

All pregnancies are reported from the time informed consent is signed until the defined follow-up period stated in Section 8.3.7.

Any report of pregnancy for any female study participant or the partner of a male participant must be reported within 24 hours to the Takeda GPSE Department using the Takeda Investigational and Marketed Products Pregnancy Report Form.

A copy of the Takeda Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Takeda medical monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage, elective abortion or congenital abnormality are considered SAEs and must be reported using the "Takeda Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol".

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the "Takeda Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol" as well as the "Takeda Investigational and Marketed Products Pregnancy Report Form". The test date of the first positive serum/urine b-hCG test or ultrasound result will determine the pregnancy onset date.

Appendix 3.9 - Abuse, Misuse, Overdose and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Appendix 3.1.

Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- Abuse – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (e.g., to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.
- Misuse – Intentional use of investigational product other than as directed or indicated at any dose. (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol.)
- Overdose – Intentional or unintentional intake of a dose of investigational product higher than the protocol-prescribed maximum dose (VWF:RCo 80 IU/kg).
- Medication Error – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of the unassigned treatment is/are always reportable as a medication error.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

All investigational product provided to pediatric subjects should be supervised by the parent/legally authorized representative/caregiver.

Appendix 3.10 - 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, these do not constitute de facto deviation from the protocol. 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 implement urgent safety measures to protect study subjects from immediate hazard to their health or safety. The measures should implement immediately and does not require prior authorization from the sponsor. In the event(s) of an apparent direct 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, and within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible EC(s) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

Appendix 3.11 - Regulatory Agency, Institutional Review Board, Ethics Committee and Site Reporting

The sponsor is responsible for notifying the relevant regulatory authorities: ***US central IRBs/EU central ECs*** of related, unexpected SAEs.

In addition the sponsor is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the rVWF program.

The investigator is responsible for notifying the local IRB/EC of SAEs or significant safety findings that occur at his or her site as required by IRB/EC procedures (see Appendix 1.5).

Appendix 3.12 – Postmarketing Experience

The most common postmarketing adverse drug reactions (ADRs) reported in association with rVWF/VONVENDI treatment include infusion-related reactions (IRR) and anaphylactic reactions. IRR may clinically manifest by the following symptoms: tachycardia, flushing, rash, dyspnea, and blurred vision. In the 2 spontaneous postmarketing cases reported as of 30 June 2021, the symptoms resolved and the patients fully recovered in 20 minutes to 4 hours upon stopping the infusion. Two post-marketing cases of anaphylactic reactions have been reported with use of VONVENDI in the post marketing setting. This ADR has never been observed in clinical trials.

APPENDIX 4. CONTRACEPTIVE GUIDANCE

Female participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described below.

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the women of childbearing potential (WOCBP) and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least [X, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment

APPENDIX 5. ABBREVIATIONS

Abbreviation	Definition
β-hCG	beta-human chorionic gonadotropin
ABR	annualized bleeding rate
ADAMTS13	A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, number 13
ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase (synonymous with SGPT)
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase (synonymous with SGOT)
AUC	area under the plasma concentration/time curve
$AUC_{0\text{-}96h}$	area under the plasma concentration/time curve from time 0 to 96 hours postinfusion/dose
$AUC_{0\text{-}\infty}$	area under the plasma concentration /time curve from time 0 to infinity
B19V	Parvovirus B19
BU	Bethesda Unit
BUN	blood urea nitrogen
BW	body weight
CB	collagen binding activity
CD4	helper T cell
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
CNS	central nervous system
COVID-19	Coronavirus Disease 2019
CRF	case report form
CRO	contract research organization

Abbreviation	Definition
DMC	data monitoring committee
DVT	deep vein thrombosis
eCRF	electronic Case Report Form
EC	ethics committee
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
EQ-5D	EuroQol-5 Dimension
EU	European Union
EUDRACT	European Union clinical trials database
FAS	full analysis set
FDA	Food and Drug Administration
Fe	Ferritin
FVIII	Factor VIII
FVIII:C	Factor VIII clotting activity
GCP	Good Clinical Practice
GI	gastrointestinal
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
Ig	immunoglobulin
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G

Abbreviation	Definition
IgM	immunoglobulin M
INR	international normalized ratio
IP	investigational product
IR	incremental recovery
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
LDH	lactic dehydrogenase
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MRI	magnetic resonance imaging
MRT	mean residence time
OD	on-demand
PBAC	pictorial blood assessment chart
PD	pharmacodynamics
pdVWF	plasma derived VWF product
pdVWF/FVIII	plasma derived VWF product containing fractions of FVIII
PEF	peak expiratory flow
PI	principal investigator
PK	pharmacokinetic(s)
PKAS	pharmacokinetic analysis set
PPAS	per protocol analysis set
PRO	patient-reported outcome
PT	prothrombin time
RSI	reference safety information
rVWF	Recombinant von Willebrand factor
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation

Abbreviation	Definition
SF-36	Short Form (36) Health Survey
SIC	subject identification code
SOC	system organ class
SWFI	sterile Water for injection
$T_{1/2}$	half-life
TEAEs	treatment-emergent AEs
T_{max}	time to maximum concentration
UHMW	ultra-high molecular weight
VAS	visual analog scale (score)
V_{ss}	apparent steady-state volume of distribution
VWF	von Willebrand factor
VWF:Ag	von Willebrand factor antigen
VWF:CB	von Willebrand Factor collagen binding activity
VWF:RCo	von Willebrand factor: Ristocetin cofactor
WBC	white blood cell

APPENDIX 6. PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Protocol Amendment 4	20 Dec 2021	Global
Protocol Amendment 3	19 May 2020	Global
Protocol Amendment 2[a]	08 Jul 2019	Global
Protocol Amendment 1	29 May 2019	Global
Original Protocol	29 Aug 2018	Global

[a] Protocol Amendment 2 did not take effect.

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