Statistical Analysis Plan

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Study Number: SHP677-304

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STATISTICAL ANALYSIS PLAN

Recombinant von Willebrand Factor (rVWF, vonicog alfa)
PHASE 3B

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)

PROTOCOL IDENTIFIER: SHP677-304

Authors: [redacted]
[redacted] (non-PK/PD sections) and [redacted] (PK/PD sections), IQVIA

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REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	2019 MAR 27	New Document
2.0	2019 APR 25	1. Update in title page "Baxalta is now part of Shire" to "Baxalta is now part of Takeda". All other mentions of Shire have been kept as the Shire templates have been used for this document. 2. Added in Section 6.2.1 that spontaneous ABR for subjects that did escalate their number of doses per week will be summarized separately for before and after the escalation. 3. Added in Section 6.2.2 that the exposure summaries will also include information on subjects that increased their number of infusions per week.
3.0	2020 JUL 07	Update IA sections per Amendments 1, 3 and other clarifications (note that Amendment 2 08JUL2019 did not take effect): 1. Update EQ-5D age details in Section 2.2.3 due to Amendment 1: EQ-5D for subjects >7 years (parent-proxy version for ages 4 to <7 years) and update 'pediatric' to 'pediatric/adolescent' 2. Update protocol date on title page and Section 1. 3. Added text to Section 4.2, SAF: '*Study Drug Administration Details* eCRF' 4. Updated Section 4.5 PKAS 5. Added details regarding paper diary and other written documentation as source data to Section 5.8 6. Added reference to tables for TEAEs occurring in ≥10% of subjects to Section 7.1 7. Added new Section 9.3 for COVID-19 8. Updated text in Section 10 Interim Analysis 9. Added text to Section 11.3 to address end of period date for IA1. 10. Added text to Section 13.0 to clarify that PKAS definition is different from protocol. 11. Minor changes to align with wording in Amendment 3. 12. Corrected error in missing day/month calculation under 3rd bullet in 11.7.1.2.2.

		13. Clarified missing date information for AEs in Section 11.7.2. 14. Corrected several typos. 15. Removed references to Sponsor assessment of relationship to IP from Section 7.1. 16. Clarified in Section 7.1 that AEs leading to discontinuation applies to both disc of IP and disc from study.
4.0	2020 OCT 14	Clarification that the primary efficacy endpoint will be based on the treated spontaneous bleeding episodes to align with protocol section 8.4.2.1. Clarified Section 11.4: transcribed data will only include eCRF data and not external data.
5.0	24 JUN 2022	**Update sections** 1, 2, 3, 4.5, 5.2, 5.5, 7.1, 7.2, 8.2.3, 9.3 and 10 per **Protocol Amendment 4.** 1. Reference to latest Protocol Amendment and date in the title page and section 1. 2. Updated Pharmacokinetic Endpoints to include all Prophylactic cohorts (1 to 4) and additional follow up visits in section 2.2.3. 3. Updated Figure 1 the study flow chart in section 3.1. The flow chart shows the additional PK/PD assessment at End of Study (EOS). 4. In Section 3.4, the sample size increased from 64 to 71 in total and pediatric subjects increased from 27 to 34. 5. Added text to Pharmacokinetic Analysis Set to specify the requirement of the completion of the washout period in section 4.5. 6. In section 5.2: Added the analysis for COVID-19 related protocol deviation. 7. Updated definition for Temporally Associated Treatment Emergent Adverse Events (TEAE). Added AEs/SAEs listing related to COVID-19 or COVID-19 vaccines in section 7.1.

		8. Added details regarding Viral Serology and pregnancy laboratory tests. Clarified/added tables and listings needed for laboratory tests. 9. Updated text to include all prophylactic cohorts (1 to 4) for PK parameters in section 8.2.3. 10. Added clarity to COVID-19 listing for missing visits due to the pandemic and which eCRF form to use in section 9.3. 11. Added clarity around use of data for the two types of interim analyses. Removed the 'ad hoc' nature of the DMC. DMC will gather at least annually and as per DMC Charter. **In Section 7.1, a table was added for TEAEs by relationship & severity by SOC & PT and added clarity regarding AE listing.** **Update based on Interim Analysis feedback** in section 6.2.2 and 7.2. In section 6.2.2 prophylactic percent compliance by comparing planned vs actual number of rVWF infusions was added. In section 7.2 box plots were added for clinical laboratory values. Due to a data issue found during routine cleaning, **adjusted EQ-5D listing presentations in section 9.1.1.** Some sites accidentally issued EQ-5D-5L instead of 3L. These results will be listed separately.
6.0	27 MAR 2024	Clarifications required based on submission related Interim Analysis and Dry Run feedback: 1. Revision history, SAP v5, bullet #6, removed details on section 5.5 CMs as this was not updated in text in final version. 2. In section 4.3, added text that if the FAS is exactly the same as the SAF, we would not repeat identical tables for the two populations. 3. In section 5.2 noted change in Protocol Deviation categories as of 16May2022 (per PDMP) 4. In Section 6.1.1 clarified the analysis subgroups.

		5. In Section 6.2.1, added historical ABR listing. Added text regarding historical ABR vs on-study ABR for Cohort 4. Added table by cause of bleed, and by cause of bleed and severity. 6. In section 6.2.2 removed sentence regarding separate ADVATE & rVWF derivations for the prophylaxis drug summaries. In section 5.7, updated section reference from 6.2.2 to 6.2 7. In section 6.2.2 added details regarding missing dose or infusion with missing date to be included in compliance calculation. Also, added tables for total rVWF and ADVATE administered. 8. In section 6.3.1 clarified table and listing to be done by surgery: major, minor, oral. Also removed that the results will be based on the first 12 months of study. Section 13 was updated accordingly as well. 9. In section 7.1, added note that if there are 0 events in overall AE tables, then the detailed tables will not be produced. 10. In section 7.1, edited details on COVID-19 vaccinations due to update in EDC/eCRF. 11. In section 7.1, TEAEs by Relationship and Max Severity has changed to Related TEAEs by Severity per shell comments. 12. In section 6.2.3 added 'with or without transfusion' to text. Added a sentence (similar to the first sentence in section 7.2) here for clarity. 13. In section 9.1.1, tweaked wording as change from baseline tables for EQ-5D were removed from shells. 14. Remove repeated summaries by VWD type in most sections except 6.1 and 9.
7.0	03 MAR 2025	After reviewing dry run 2, updates were requested. 1. In section 4.4, added text that if the PPAS is exactly the same as the SAF, we would not repeat identical tables for the two populations. 2. In section 4.5, clarified that PK/PD assessments are for prophylaxis cohorts. 3. In section 5, added a general statement that select tables will be repeated by age group, if required. The selection could span many sections. In section 6.2.1:

		4. Added to assessment of efficacy of on-demand treatment, dose of rVWF or ADVATE per infusion per bleed. 5. Added new table for menstrual/heavy bleed location by females of childbearing potential. 6. Clarified treated sABR before and after *prophylaxis* dose escalation & noted not to summarize by study period. 7. Added historical BEs for cohort 4 to categorized sABR. 8. Modified time to first bleeding event to time to first *spontaneous* bleeding event. 9. Added percent change from historical baseline for cohort 4 summary. 10. In section 6.2.3 added a line plot for individual subject ferritin levels over time. 11. In section 6.3.1 added by age group to surgery summaries. 12. In section 7.2 added ferritin to list of hematology tests. 13. In section 8.2.3 clarified which parameters would be calculated at initial and EOS assessments. 14. In section 9, added prophylaxis initiation timepoint to tables of observed values.

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ABBREVIATIONS

Ab	antibodies
ABR	annualized bleeding rate
ADAMTS13	A disintegrin and metalloproteinase with a thrombospondin type 1 motif, number 13
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
$AUC_{0\text{-}96hr}$	area under the concentration versus time curve from 0 to 96 hours post-infusion
$AUC_{0\text{-}\infty}$	area under the concentration versus time curve from 0 extrapolated to infinity
BE	bleeding episode
BLQ	below the limit of quantification
CD4	helper T cell
CHO	Chinese hamster ovary
CI	confidence interval
CL	total body clearance
C_{max}	maximum observed concentration
COVID-19	Coronavirus Disease 2019
CTMS	clinical trial management system
DMC	data monitoring committee
eCRF	electronic case report form
eDiary	electronic diary
ENR	all subjects enrolled set
EOS	end of study
EQ-5D-3L	EuroQoL five dimension questionnaire, three level
FAS	full analysis set
FVIII	factor eight
FVIII:C	factor VIII clotting activity
GI	gastrointestinal
HIV	human immunodeficiency virus
HRQoL	health-related Quality of Life
IgG	immunoglobulin G
IP	investigational product
IR	incremental recovery
LDH	lactate dehydrogenase
MCH	mean corpuscular hemoglobin

MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRT	mean residence time
OD	on-demand
PCS	potentially clinically significant
PD	pharmacodynamic
PK	pharmacokinetic
PKAS	pharmacokinetic analysis set
PPAS	per-protocol analysis set
RBC	red blood cells
rFVIII	recombinant factor eight
rVWF	recombinant von Willebrand factor
SAE	serious adverse event
SAS	safety analysis set
SAP	statistical analysis plan
SF-36	short form (36) health survey
SOC	system organ class
$t_{1/2}$	terminal half-life
TBL	total bilirubin
TEAE	treatment emergent adverse event
t_{max}	time to reach C_{max}
TSQM-9	nine-item Treatment Satisfaction Questionnaire for Medication
VAS	visual analog scale
V_{ss}	volume of distribution at steady state
VWD	von Willebrand disease
VWF	von Willebrand factor
VWF:Ac	von Willebrand factor activity
VWF:Ag	von Willebrand factor antigen
VWF:CB	von Willebrand factor collagen binding activity
VWF:RCo	von Willebrand factor: ristocetin cofactor
V-WIQ	von Willebrand impact questionnaire
WBC	white blood cells
WHO-DD	World Health Organization - Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy, safety, pharmacokinetic (PK) and pharmacodynamic (PD) data, and health-related Quality of Life (HRQoL) measures described in the final study protocol Amendment 4.0 dated 20 Dec 2021. Specifications for tables, figures, and listings are contained in a separate document.

2. OBJECTIVES, ESTIMAND(S), AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

To evaluate the efficacy of recombinant von Willebrand factor (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.

The annualized bleeding rate (ABR) will be assessed based upon each individual spontaneous bleed, requiring coagulation factor replacement therapy, i.e., rVWF treatment (Protocol section 8.4.2.1). Hereafter these bleeding episodes (BEs) will be referred to as "**treated BEs**".

2.1.2 Secondary Objectives

- To evaluate the long-term safety of rVWF 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 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 for on-demand (OD) treatment of bleeding episodes (spontaneous and traumatic) in adult and pediatric subjects.

2.1.3 Exploratory Objectives

In adult and pediatric subjects treated with rVWF:

- To obtain additional data on the efficacy of perioperative bleeding management with rVWF if surgery is required.

- To assess pharmacokinetics (PK) and pharmacodynamics (PD) of rVWF and to monitor incremental recovery (IR) of rVWF over time in adult and pediatric subjects.
- To assess HRQoL data, treatment satisfaction and health resource utilization over time for subjects receiving rVWF prophylaxis.

2.2 Endpoints

2.2.1 Primary Endpoint

Spontaneous ABR during prophylaxis treatment with rVWF based on the data collected during the first 12 months on study treatment.

2.2.2 Secondary Endpoints

Safety:

- AEs/ serious AEs (SAEs): incidence, severity, causality.
- Occurrence of thromboembolic events.
- Occurrence of hypersensitivity reactions.
- Immunogenicity:
  a) Development of neutralizing antibodies (inhibitors) to von Willebrand factor (VWF) and factor eight (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 while enrolled in the study.
- Categorized weekly number of infusions defined as 1, 2, or ≥3 during prophylactic treatment with rVWF.
- Categorized spontaneous ABR defined as 0, > 0 to ≤ 2, > 2 to ≤ 5, or > 5 bleeding episodes during rVWF 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.
- Total number of infusions and the average number of infusions per week during prophylactic treatment with rVWF.
- Total weight adjusted consumption of rVWF during prophylactic treatment.
- Transfusion free maintenance of hemoglobin and plasma 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 and ADVATE (recombinant factor eight [rFVIII], octocog alfa) utilized to treat bleeding episodes while enrolled in the study.
- Weight-adjusted consumption of rVWF and ADVATE (rFVIII, octocog alfa) per bleeding episode while enrolled in the study.

2.2.3 Exploratory Endpoints

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 or at day 14 post operation, whichever occurs first.
- Daily intra-and postoperative weight-adjusted dose of rVWF with or without ADVATE through postoperative day 14.

Pharmacokinetic Endpoints:

- Pharmacokinetic parameters, where possible, including initial assessment for Cohorts 4 and EOS steady-state assessment for Cohort 1 to 4: IR, terminal half-life ($t_{1/2}$), mean residence time (MRT), area under the concentration versus time curve (AUC) from 0 extrapolated to infinity ($AUC_{0-\infty}$), AUC from 0 to 96 hours post-

infusion ($AUC_{0\text{-}96hr}$), maximum observed concentration (C_{max}), time to reach C_{max} (t_{max}), volume of distribution at steady state (V_{ss}) and total body clearance (CL) for VWF:ristocetin cofactor (VWF:RCo), VWF:antigen (VWF:Ag), and VWF:collagen binding activity (VWF:CB). The corresponding PD of rVWF as measured in FVIII clotting activity (FVIII:C) will be assessed using C_{max}, t_{max}, and $AUC_{0\text{-}96hr}$.

- 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 end of study (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™ (PedsQL™) and parent proxy version
       - 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)
- Treatment Satisfaction: 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.

3. STUDY DESIGN

3.1 General Description

This is a phase 3b, prospective, open-label, uncontrolled, non-randomized, multicenter study evaluating long-term safety and efficacy of rVWF for prophylaxis and OD treatment of bleeding episodes in pediatric and adult subjects with severe von Willebrand disease (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 in this Phase 3b extension study.

On-demand treatment arm cohorts:

5. Pediatric subjects 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.

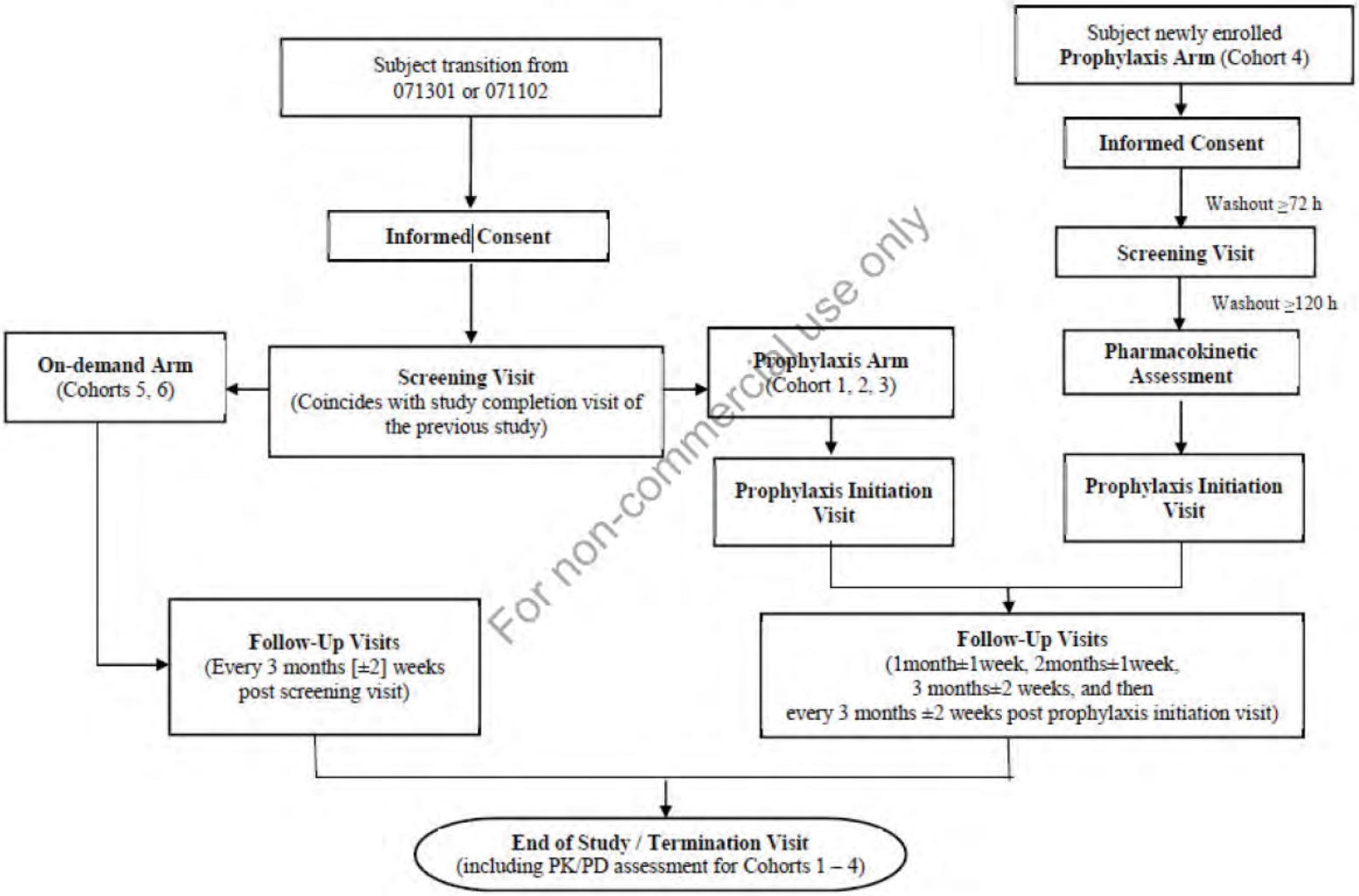
During the entire study period, bleeding episodes requiring substitution therapy with VWF concentrate will be treated with rVWF with or without ADVATE.

If surgery is needed subjects will receive rVWF, with or without ADVATE, for management of perioperative bleeding.

Subjects will be observed for a minimum of 12 months.

A study flow chart detailing the study design is presented in Figure 1 Study Flow Chart.

Figure 1 Study Flow Chart



3.2 Randomization

This is a non-randomized clinical study.

3.3 Blinding

This is an open label clinical study.

3.4 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 prophylactic 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.

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 European Medicines Agency Guideline on Clinical Investigation of Human Plasma Derived von Willebrand Factor Products (CPMP/BPWG/220/02).

4. STATISTICAL ANALYSIS SETS

4.1 All Subjects Enrolled Set

The all subjects enrolled set (ENR) will consist of all subjects who have signed informed consent (either from subject or from subject's legally acceptable representative) as obtained from the *Screening* electronic case report form (eCRF).

4.2 Safety Analysis Set

The safety analysis set will consist of all subjects who received any amount of rVWF as obtained from the investigational product (IP) administration electronic diary (eDiary), *Study Drug Administration Details* eCRF or *Pharmacokinetic Infusion* eCRF.

4.3 Full Analysis Set

The full analysis set (FAS) will consist of all subjects who satisfy all entry criteria and received any amount of IP. If all subjects satisfy all entry criteria and the FAS consists of the same subjects as the safety analysis set; then only the one set of outputs for the safety

analysis set will be presented (i.e. items such as baseline demographics or screening characteristics will not be repeated).

4.4 Per-protocol Analysis Set

The per-protocol analysis set (PPAS) will consist of all subjects included in the FAS that have no major/critical protocol violations that may have an impact on the efficacy assessment of the IP. If the PPAS consists of the same subjects as the safety analysis set; then only the one set of outputs for the safety analysis set will be presented (i.e. items such as baseline demographics or screening characteristics will not be repeated).

All protocol deviations to be considered for the PPAS will be obtained from the IQVIA managed Clinical Trial Management System (CTMS). Prior to performing any analysis as set out in this SAP, a meeting will be held to discuss all major/critical deviations entered in CTMS and what the impact on efficacy data may be. A decision will be made at this meeting whether a specific deviation will lead to the subject's exclusion from the PPAS. It should therefore be noted that not all major protocol deviations will necessarily result in an exclusion of a subject from the PPAS. As protocol deviations from CTMS will be used to determine eligibility for the PPAS all efforts should be made to ensure that the deviations in CTMS are complete and finalized by the time of this meeting. This meeting will be attended by participants from at least Biostatistics and Clinical Development (including medical monitors/advisors) from both IQVIA and Takeda. Decisions made during this meeting must be signed off before performing any analysis as set out in this SAP.

4.5 Pharmacokinetic (PK)/Pharmacodynamic (PD) Analysis Set

The PK/PD analysis set (PKAS) will be composed of all subjects in prophylaxis cohorts (1 to 4) who completed the required washout period, received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post-dose measurement for pharmacokinetic and/or pharmacodynamic analysis. The subject should not be actively bleeding at the time of PK assessment.

PK/PD samples with unknown dosing time, unknown actual or planned collection date/time, or where the concentration could not be determined, or where the results were biologically implausible, will be excluded from the Pharmacokinetic/Pharmacodynamic analysis and the reasons for exclusion will be documented (refer to Section 5.2).

5. STUDY SUBJECTS

Select tables will be presented by age groups, if deemed necessary.

5.1 Disposition of Subjects

A listing of all screen failures (i.e., subjects who were screened but not dosed) will be presented along with reasons for screen failure. A separate listing presenting inclusion/exclusion criteria not met will also be presented for the ENR.

The number of subjects who were included in and excluded from each defined analysis set (refer to Section 4) will be summarized by cohort. Inclusion and exclusion from each defined analysis set, including the reason for exclusion from the analysis set will be listed for the ENR.

The number and percentage of subjects who completed and prematurely discontinued during the study will be summarized for each cohort for the safety analysis set. Reasons for premature discontinuation as recorded on the C*ompletion/Termination* page of the eCRF will be summarized (number and percentage) by cohort for the safety analysis set. All subjects who completed and prematurely discontinued the study will be listed for the ENR.

The number of subjects enrolled, dosed and completed will be tabulated by site and country. In addition, the duration of enrollment, in days, will be summarized for each site, country, and overall. Duration of enrollment will be calculated as (last date of contact for any subject at that site - the first date of informed consent for any subject at that site + 1).

Previous studies subjects participated and the cohort the subjects is included in for this study will be listed for the ENR.

5.2 Protocol Deviations

Protocol deviations will be recorded in the IQVIA CTMS and will be classified as critical, major, or minor. A biostatistical review of the protocol deviations will be performed prior to any analysis presenting protocol deviations.

Critical/major/minor deviations will be summarized by category, site, and cohort for the safety analysis set. Protocol deviations will be listed for the safety analysis set. A subset of the summary by deviations associated with/related to COVID-19 will also be presented.

Deviation categories will be included as part of the CTMS protocol deviations log and may include any of the following categories:

- Informed consent
- Eligibility and entry criteria
- Concomitant medication criteria
- Laboratory assessment criteria
- Study procedures criteria
- Serious AE criteria
- Visit schedule criteria
- Investigational product compliance
- Efficacy criteria
- Administrative criteria
- Source document criteria
- Regulatory or ethics approval criteria
- Other criteria.

Protocol deviation categorizations changed as of 16 May 2022 per the Protocol Deviation Management Plan (PDMP). Any deviations that occurred up to 15 May 2022 will follow the old categorization as shown above, and deviations from 16 May 2022 forward will follow the new categorization (i.e. historical data will not be re-categorized after updates are made to the PDMP). The CTMS log has both categorizations based on the date of occurrence. The protocol deviation summary and listing will be presented by the old categories by mapping of new categories to the old categories.

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

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

Affected data will be evaluated by the pharmacokineticist to determine whether they can be included in the PK analysis. Subjects and/or data with important deviations or other data issues that are not included in the PKAS will be reported in listings, along with the reason for exclusion. Other changes to the procedures or events which do not impact the quality of the PK data will not be considered significant protocol deviations for the evaluation of PK. A common example of a non-significant protocol deviation is a deviation from the prespecified blood collection times.

5.3 Demographic and Other Baseline Characteristics

Descriptive summaries of demographic and screening characteristics will be presented by cohort for the safety analysis set, FAS, PPAS, and PK Set. Demographic and screening characteristics will be listed for the safety analysis set.

Demographic variables will include age, race, ethnicity, and childbearing potential for female subjects as reported on the *Demography* eCRF. For summary purposes, age will be categorized as follows:

- Subjects age < 6 years (OD cohort only)
- Subjects age ≥ 6 and < 12 years (OD cohort only)
- Subjects aged ≥ 12 and < 18 years
- Subjects aged ≥ 18 years

Screening characteristics to be summarized and listed will be the corresponding value to which the subject was enrolled onto the study. These values will include the following:

- Results obtained from the *Vital Signs* eCRFs:
  - Height
  - Weight
- Results obtained from the *Von Willebrand Disease* eCRF:
  - Von Willebrand Disease type
- Results obtained from the *Genetic Testing and Genetic Testing History* eCRFs:
  - Blood group and rhesus factor
- Pregnancy test results from the *Pregnancy Test* eCRF.
- Results obtained from the central laboratory:
  - VWF:RCo
  - VWF:Ag
  - VWF:CB
  - FVIII:C

- VWF Inhibitor
- FVIII Inhibitor
- Platelets
- Prothrombin time
- International normalized ratio
- Activated partial thromboplastin time
- Human immunodeficiency virus (HIV) and helper T cell (CD4) results if HIV positive
- Alanine aminotransferase (ALT)
- Albumin
- Creatinine

Screening characteristics to be listed only are:

- Results obtained from the *Genetic Testing and Genetic Testing History* eCRFs:
  - VWD gene mutation
  - Multimer pattern
  - A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, member 13 (ADAMTS13) activity

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

$$BMI(kg/m^2) = \frac{weight(kg)}{height(m)^2}.$$

5.4 Medical History

Medical history will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) as specified in the data management coding guidelines.

Medical history as collected on the *Medical History* eCRF will be summarized by system organ class, preferred term, and cohort for the safety analysis set. A listing presenting medical history will be presented for the safety analysis set.

5.5 Prior and Concomitant Medications, Non-drug Therapies and Procedures

All data on medications, non-drug therapies and procedures will be obtained from the *Concomitant Medication/Non-drug Therapy* eCRF and will be coded using the version of

the World Health Organization – Drug Dictionary (WHO-DD) as specified in the data management coding guideline.

Medications, non-drug therapies and procedures will be assigned to prior or concomitant using the following rules:

- Prior: if the medication, non-drug therapy or procedure stopped prior to first IP administration in this continuation study.
- Concomitant: if the medication, non-drug therapy or procedure:
  - started after first IP administration in this continuation study; or
  - started before the first IP administration in this continuation study and ended after the first IP administration in this continuation study.

Missing or partial dates will be imputed as described in Section 11.7.1 prior to determining whether the medication, non-drug therapy or procedure is prior or concomitant.

Prior and concomitant medications will be summarized by therapeutic class, preferred term, and cohort for the safety analysis set. No summaries will be produced for non-drug therapies or procedures. Prior and concomitant medications, non-drug therapies and procedures will be listed for the safety analysis set.

5.6 Von Willebrand Treatment History

Data as obtained from the *Von Willebrand Prophylactic Treatment History* which collects the use of plasma derived VWF products in the 12 months prior to Screening will be coded using the version of WHO-DD as specified in the data management coding guidelines. Von Willebrand Prophylactic products taken in the 12 months prior to Screening as reported in the eCRF will be listed for the safety analysis set.

Bleeding history and the Von Willebrand Treatment received to treat bleeds in the 12 months prior to Screening will be reported on the *Von Willebrand Treatment and Bleeding History* eCRF. Bleeding history and on-demand treatment of VWF will be listed for the safety analysis set.

5.7 Exposure to Investigational Product

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

transcribed into the eCRF. The e-diary, paper diary, and other written documentation is all recognized as source documentation for infusions.

Exposure to rVWF and ADVATE forms part of the secondary efficacy endpoints is further described in Section 6.2.2.

5.8 Measurements of Treatment Compliance

Compliance is described as part of the exposure to IP in Section 6.2.2.

6. EFFICACY ANALYSES

All efficacy analyses will be based on the FAS unless stated otherwise.

No formal statistical tests will be performed for this study.

6.1 Analyses of Primary Efficacy Endpoint

6.1.1 Spontaneous Annualized Bleeding Rate

The primary efficacy endpoint for this study is the ABR for spontaneous (as assessed by the investigator) BEs requiring treatment with a VWF product during the first 12 months (as defined in Section 11.3) of prophylactic treatment with rVWF.

Details on bleeding episodes will be entered by the subject in the eDiary. The site will perform a review of eDiary data, and the Investigator assessment of the bleeding and treatment will be recorded in the eCRF. For the purposes of analyses the Investigator assessed bleeding data will be used for the analysis of efficacy.

Descriptive statistics on bleeding episodes, including site, cause and severity will be presented.

The ABR for treated spontaneous BEs will be derived as

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

where the observation period in years for the first 12-month period is derived as

$$Observation\ Period\ (years) = \frac{12\ Month\ End\ Date - Date\ of\ First\ Infusion + 1}{365.2425}.$$

The 12-month end date is defined in Section 11.3.

Bleeds of unknown causality will be considered as spontaneous bleeds.

The ABR for treated spontaneous BEs will be analyzed descriptively, including 2-sided 95% Confidence Intervals (CI) around the mean and will be assessed on each cohort receiving prophylactic treatment. If the lower bound of the CI is negative, replace it with zero. Results will be presented by VWD type, study periods, and age group.

As sensitivity analysis, the primary efficacy endpoint will be presented for the PPAS as well.

6.2 Analyses of Secondary Efficacy Endpoints

All secondary efficacy endpoints will be analyzed by age group, and cohort on the first 12-month data and the entire study period. For the purposes of analyses the Investigator assessed bleeding data will be used for analysis, if applicable. Mean, standard deviation, median, range, quartiles will be calculated for continuous endpoints. CIs around the mean at the 95% level will be provided when appropriate. Proportions will be calculated for categorical endpoints and expressed as percentages in tables.

6.2.1 Bleeding Episodes

The secondary efficacy endpoints related to bleeding episodes are:

To assess efficacy of prophylaxis:

- The ABR for treated spontaneous BEs under prophylactic treatment with rVWF over the entire study period.
- Categorized treated spontaneous ABR.
- Treated spontaneous ABR by bleeding location.
- Time to first spontaneous bleeding event under each prophylactic regimen.

To assess efficacy of on-demand treatment:

- Overall hemostatic efficacy rating at resolution of bleed.
- Number of infusions of rVWF and ADVATE to treat bleeding episodes.

- Weight-adjusted consumption of rVWF and ADVATE per bleeding episode while enrolled in the study.
- Average Dose of rVWF and ADVATE per infusion per bleed (IU/kg).

The on-study ABR for treated spontaneous BEs will be derived separately for each location of bleed using the same formula as described in Section 6.1.1. Treated spontaneous ABR for each location of bleed will be summarized descriptively, including 2-sided 95% CIs around the mean. For the menstrual/heavy menstrual bleed location, treated spontaneous ABR will be summarized for females of childbearing potential.

Similarly, treated spontaneous ABR will be summarized separately for subjects that escalated the number of infusions required per week. The summary will include the treated spontaneous ABR before and after the prophylaxis dose escalation and will not be presented by study period.

The ABR for treated spontaneous BEs as described in Section 6.1.1 will be categorized as follows:

- 0 bleeds/year
- > 0 to ≤ 2 bleeds/year
- > 2 to ≤ 5 bleeds/year
- > 5 bleeds/year

Categories will be summarized descriptively including 2-sided 95% Wald CIs determined from using the SAS® code in Section 15.2.1. The summary will include historical BEs for cohort 4.

Analysis time for the analysis of time to first spontaneous bleeding episode (in days) will be derived as:

$$\begin{aligned} &Analysis\ Time\ (Days) \\ &\quad = Date\ of\ First\ Spontaneous\ Bleed(or\ Censoring) \\ &\quad - Reference\ Start\ Date + 1 \end{aligned}$$

where the reference start date is defined in Section 11.2.

Time to first spontaneous bleed will be analyzed using Kaplan-Meier by regimen (once weekly, twice weekly, 3 times a week, and other), and cohort at time of bleed, for each

study period. Subjects with 0 bleeds during each study period being analyzed will be censored at the last day within that study period (defined in Section 11.3). The time to first bleed for censored results will be derived using the date of censoring and the record will be flagged as being censored for analysis purposes. The SAS® code in Section 15.2.3 will be used to analyze time to first bleed.

Kaplan-Meier results will be summarized and presented graphically by prophylactic cohort and age group.

For on-demand treatment of BEs, descriptive statistics of BE characteristics and treatment efficacy rating, as well as drug consumption (number of infusions and weight-adjusted dose to treat bleeds) will be presented.

In addition to protocol specified analyses, historical bleed data was captured for cohort 4 (as noted in Section 5.6) and outputs for this cohort will be specified here. For treated BEs, the bleeding history (cohort 4) will be summarized using descriptive statistics by cause of bleed (any, spontaneous, trauma, surgery, other). Both the historical and on-study data will be characterized with the change from historical baseline and the percent change from historical baseline displayed for the first 12-months data and the entire study period. Historical ABR will be listed for cohort 4. A summary table of the number of BEs by study period, cause of bleeding, and severity will be provided for cohort 4. For each cause of bleeding, the total number of recorded episodes and the number and percentage of episodes by severity level (within cause) will be presented for cohort 4. Both the historical and on-study data will be characterized.

6.2.2 Exposure and Compliance to Investigational Product

The secondary efficacy endpoints related to prophylaxis exposure and compliance to IP are:

- Categorized weekly number of infusions defined as 1, 2, or ≥ 3 during prophylactic treatment with rVWF.
- Total number of infusions and the average number of infusions per week during prophylactic treatment with rVWF.
- Total weight-adjusted consumption of rVWF during prophylactic treatment per week, and weight-adjusted dose per prophylactic infusion.

Details on study drug administration will be entered by the subject in the eDiary. The site will perform a review of eDiary data and should any information be incorrect will

document corrections in the eCRF. For the purposes of analyses the Investigator corrected data will take preference above what was entered by the subject in the eDiary.

Listings on IP administration and compliance to IP will be presented on the safety analysis set while summaries will be presented on the FAS.

Summaries on the prophylactic cohorts will be presented by cohort (1 to 4) and regimen (once a week, twice a week, 3 times a week, and other).

The following derivations will be performed separately for each reason of infusion and overall. Derivations will be performed for each study period as defined in Section 11.3.

The average number of infusions per week will be derived as

$$Avg\ infusions\ per\ week = \frac{Total\ Number\ of\ Infusions\ in\ Period}{Observation\ Period\ (Days)} \times 7$$

where the observation period in days is defined as

$$Observation\ Period\ (Days) = Last\ Day\ of\ Period - Reference\ Start\ Date + 1.$$

The last day of each period is defined in Section 11.3 and the reference start date in Section 11.2.

The average number of infusions per week will be categorized as follows:

- ≥ 0 to < 1 infusion per week
- ≥ 1 to < 2 infusions per week
- ≥ 2 to < 3 infusions per week
- ≥ 3 infusions per week

The categorized number of infusions per week will only be derived and presented for rVWF. The presentation will also include the number of subjects that escalated their number of infusions per week (i.e., move from a lower category to any higher category based on the ordering of the above bulleted list). The prophylactic percent compliance to rVWF per subject will compare the number of planned versus actual number of rVWF infusions and will be derived as follows for prophylactic cohorts:

$$Compliance\ (\%) = \frac{Sum\ of\ All\ Actual\ Prophylaxis\ Infusions}{Sum\ of\ All\ Planned\ Prophylaxis\ Infusions} \times 100.$$

Total dose in IU/kg will be defined as the sum of the doses of each individual infusion, while the average dose in IU/kg will be the total dose divided by the number of infusions.

Compliance to prophylactic doses will be calculated relative to the Investigator entered planned dose and will be derived as

$$Compliance\ (\%) = \frac{Sum\ of\ All\ Actual\ Prophylaxis\ Doses}{Sum\ of\ All\ Planned\ Prophylaxis\ Doses} \times 100.$$

Infusions with partial information will be included in the compliance calculations, (e.g., if the dose amount (IU/kg) or if the infusion date is missing).

Additionally, the total rVWF and ADVATE administered during the study will be summarized for the safety analysis set. This will include the total number of doses administered overall and by reason for treatment, total number of prophylactic infusions, total number of exposure days overall and by reason for treatment, total amount of study drug (IU) administered to subjects during the study, overall and by reason for treatment, and the cumulative weight-adjusted dose (IU/kg) per subject. Exposure days are defined as the number of unique calendar days when a subject received any dose.

6.2.3 Transfusion Free Maintenance of Hemoglobin and Plasma Ferritin Levels

All transfusions given during the study will be summarized and listed for the FAS. Concomitant medication data will be reviewed by the medical team to identify whether a specific concomitant medication should be considered as a transfusion for analysis purposes.

The number and proportion of subjects that required no transfusion to maintain hemoglobin level will be summarized by cohort and age group.

Plasma ferritin levels will be summarized in a similar fashion as described for clinical laboratory data described in Section 7.2. Descriptive statistics for plasma ferritin levels as obtained and changes from baseline at each assessment time point will be presented by cohort and age group. For each subject the plasma ferritin levels over time will be plotted.

6.3 Analysis of Exploratory Endpoint

6.3.1 Perioperative Management of Bleeding

The exploratory efficacy endpoints related to the perioperative management of bleeding are:

- 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 or at day 14 post operation, whichever occurs first.
- Daily intra- and postoperative weight-adjusted dose of rVWF with or without ADVATE through postoperative day 14.

Results for perioperative management of bleeding will be listed and summarized by surgery (overall, major, minor and oral) and by age group for the FAS. All results will be based on the data of the entire study.

The percentage of actual versus predicted blood loss will be determined as

$$Actual\ vs.\ Predicted(\%) = \frac{Actual\ Blood\ Loss}{Predicted\ Blood\ Loss} \times 100.$$

The percentage of actual versus predicted blood loss will not be presented if there is no predicted blood loss.

Total weight-adjusted dose (IU/kg) will be determined by timepoint and reason of infusion (preoperative priming infusion, preoperative loading dose, intraoperative, and postoperative). Total weight-adjusted dose (IU/kg) will also be determined for perioperative dosing, where perioperative is defined as anything post first incision up to discharge from hospital after the surgery.

For postoperative and perioperative dosing, the daily weight-adjusted dose will be determined as the sum of all doses received per day per surgery. Per surgery an average of these daily weight-adjusted doses will also be presented in analyses.

7. SAFETY ANALYSIS

The safety analysis will be performed using the safety analysis set. Safety variables include AEs, clinical laboratory variables, and vital signs. For each safety variable, the last value collected before the first dose of IP will be used as baseline for all analyses of that safety variable. All safety analyses will be performed overall, by age group, and cohort on study periods as described in Section 11.3.

7.1 Adverse Events

Adverse events as recorded on the *Adverse Event* eCRF will be coded using the MedDRA version specified in the data management coding guidelines.

An AE will be considered a treatment emergent AE (TEAE) if it has a start date during or after the first dose of IP administration on this study.

A TEAE will be considered as a temporally associated TEAE if it starts during infusion or within 24 hours (or 1 day if time is not available) after completion of last IP infusion.

TEAEs will be considered as related to IP as assessed by the Investigator if indicated as "Probably Related" or "Possibly Related" on the eCRF.

An overall summary of the number of subjects with TEAEs as well as the number of events will be presented, including the number and percentage of subjects with any TEAEs, serious TEAEs, fatal TEAEs, TEAEs related to IP, TEAEs related to procedure, TEAEs leading to discontinuation of IP (rVWF, ADVATE), TEAEs leading to discontinuation from study, temporally associated TEAEs, allergic reaction TEAEs, local and systemic TEAEs, thromboembolic TEAEs, and severe hypersensitive reaction TEAEs. All categories are as collected on the eCRF except for temporally associated TEAEs which is defined above. If any category in the overall summary table has no events, then the detailed table summaries will not be displayed (e.g. if there 0 fatal TEAEs, then these summaries by the various subgroups will **not** be displayed simply to state 'no observations').

A two-sided 95% CI will be calculated for thromboembolic TEAEs and severe hypersensitive reaction TEAEs using a Clopper-Pearson test using the SAS® code in Section 15.2.2.

The number and percentage of subjects reporting TEAEs, as well as the number of events, in each cohort and age group will be tabulated by system organ class (SOC) and

preferred term; by SOC, preferred term, and maximum severity. TEAEs considered related to IP will be summarized by SOC and preferred term. Related TEAEs by severity will be summarized by SOC and preferred term.

The number of TEAEs that occur in ≥10% of subjects will be summarized by preferred term and by preferred term within SOC.

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

Imputations for missing AE data will be handled as described in Section 11.7.

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

All TEAE data will be listed for the safety analysis set. The listing of all TEAEs 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.

COVID-19 associated/related TEAEs will be listed by searching for terms 'COVID-19', 'COVID', 'coronavirus' or 'SARs-CoV-2'. COVID-19 vaccinations related complications or TEAEs will be recorded on the *Adverse Event* eCRF and will be listed.

The following derivations based on eCRF reported data will be performed:

Duration of AE:

The duration of AE using unimputed dates will be calculated as:

$$Duration\ (Hours) = AE\ Stop\ Date\ and\ Time - AE\ Start\ Date\ and\ Time$$

if time is available for both the start and stop dates of the AE. The duration will be presented in hours should the result be ≤ 24 hours. If the result is > 24 hours the result will be presented in days as described below.

If time is missing for either the start date or the stop date of the AE, or the duration as calculated above resulted in > 24 hours, then the duration will be presented in days, calculated as follows:

$$Duration\ (Days) = AE\ Stop\ Date - AE\ Start\ Date + 1.$$

If either the start date or stop date is partial or completely missing, no duration will be calculated.

Time since last IP administration:

Time since last IP administration will only be presented for TEAEs. The last IP administration is defined as the IP immediately preceding the start of the AE. The start date and time of the preceding IP administration will be used for all calculations.

Time since last IP administration will be calculated as:

$$Time\ Since\ Admin\ (Hours) = AE\ Start\ Date\ and\ Time - Dose\ Date\ and\ Time$$

if time is available for both the start date of the AE and the IP administration. Time since last administration will be presented in hours if the result is ≤ 24 hours. If the result is > 24 hours the result will be presented in days as described below.

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

$$Time\ Since\ Admin\ (Days) = AE\ Start\ Date - Dose\ Date + 1.$$

Annualized rates:

The annualized rates for thromboembolic TEAEs and severe hypersensitive reactions will be determined as follows:

$$Rate = \frac{Number\ of\ TEAEs}{Duration\ (years)}$$

where duration (years) is the duration in years within the specific period being analyzed as described in Section 11.3.

7.2 Clinical Laboratory Data

Descriptive statistics for clinical laboratory values as obtained from the central laboratory (in standardized units) and changes from baseline at each assessment time point will be

presented by cohort and age group. The descriptive statistics for clinical laboratory values (observed) and change from baseline will be displayed for each parameter by box plots over time overall, by cohort, and age group. Results obtained from local laboratories will not be included in summaries. The only pre-dose results that will be presented in summaries will be the baseline result as defined in Section 11.5.

The following laboratory tests will be included in summaries:

Chemistry Creatinine, 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 Cells [RBC]), Leukocytes (White Blood Cells [WBC]), Hemoglobin, Hematocrit, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), WBC Differential Count (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils), Platelets, Ferritin.

Urinalysis Specific gravity, Urobilinogen, Ketones, pH, Protein, Bilirubin, Nitrite, Glucose, Erythrocytes.

Coagulation Prothrombin Time, International Normalized Ratio, activated thromboplastin time, VWF:RCo, VWF:Ag, VWF:CB, FVIII:C.

Immunogenicity 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.

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).

All laboratory data (including data from local laboratories [as obtained from the eCRF], data at unscheduled visits and data from tests not mentioned above) will be listed for the safety analysis set. Abnormal laboratory results will be listed for the safety analysis set.

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

For hematology, and clinical chemistry parameters shift tables will be presented for the safety analysis set. Shift tables from baseline to Month 12, Month 24 and End of Study visits will be presented in terms of whether the result is low, normal, or high when compared to the normal ranges as well as in terms of clinical significance as rated by the Investigator. For coagulation parameters summary statistics for observed values and change from baseline at planned timepoints will be presented for the safety analysis set. Shift tables are not planned for coagulation parameters. Results during PK assessment will not be included in clinical laboratory data outputs, but in PK specific outputs as described in Section 8.

Clinically Significant abnormal values in laboratory parameters will be summarized. Descriptive statistics for immunogenicity (i.e. a positive result), viral serology, urinalysis and pregnancy results will be presented for the safety analysis set. Only scheduled results will be presented in summaries.

7.3 Vital Signs

Descriptive statistics for vital signs (e.g., systolic and diastolic blood pressure, pulse rate, and body weight) as reported on the *Vital Signs* eCRFs and their changes from baseline at each post-baseline visit and at the end of study will be presented by cohort, age group and overall.

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

Table 1: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign Parameter	Flag	Change from Baseline
Systolic blood pressure (mmHg)	High	Increase of ≥20
	Low	Decrease of ≥20
Diastolic blood pressure (mmHg)	High	Increase of ≥15
	Low	Decrease of ≥15
Pulse rate (beats per minute)	High	Increase of ≥15
	Low	Decrease of ≥15
Weight (kg)	High	Increase of ≥7%
	Low	Decrease of ≥7%

All vital signs data will be listed for the safety analysis set.

7.4 Electrocardiogram

Electrocardiogram results and interpretation by the Investigator are entered on the *Electrocardiogram* eCRFs. The results (normal/abnormal) will be summarized by cohort, while the results and interpretation will be listed for the safety analysis set.

7.5 Other Safety Data

No other safety assessments/variables are planned for this study.

8. PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS

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

All summaries and analyses of the PK/PD data will be based on the PK/PDAS as defined in Section 4.5 unless specified otherwise.

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

If any concentration/activity 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.

VWF and FVIII activity data, observed and pre-infusion-corrected, will be summarized by assessments (initial and end of study) using descriptive statistics. Plots of arithmetic mean observed and pre-infusion-corrected (refer to Section 8.2) VWF:RCo, VWF:Ag, VWF:CB and FVIII activity-time data (±SD, as appropriate) will be presented by assessments (initial and end of study) on linear and semi-logarithmic scales. Individual subject observed VWF:RCo, VWF:Ag, VWF:CB and FVIII activity-time data will be graphically presented on linear and semi-logarithmic scales.

8.1 Handling Below Limit of Quantitation (BLQ) Values

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

8.2 Pharmacokinetic Parameters

8.2.1 General

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

concentration could not be determined, or where biologically implausible will be excluded from the analysis.

8.2.2 Pre-infusion Correction

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

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

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

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

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

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

where $C_{measured,pre\text{-}infusion}$ is the pre-infusion concentration, $C_{max,measured}$ is the maximum concentration measured post dose and $C_{measured,t}$ is the measured concentration at time t.

Following baseline-correction, any pre-infusion value will be set to zero.

Pre-infusion correction for FVIII will be based only on the first equation regardless of VWD type.

8.2.3 Calculated Pharmacokinetic Parameters

The following PK parameters, based on serial PK samplings and pre-infusion corrected concentration levels, will be calculated for VWF:RCo, VWF:Ag, and VWF:CB and

reported by assessments (initial and end of study) using descriptive statistics for each adult subject and for each pediatric subject when applicable in Cohorts 1, 2, 3, or 4:

$AUC_{0-\infty}$	Area under the concentration versus time curve from 0 extrapolated to infinity after a single dose using linear Trapezoidal Linear/Log interpolation calculation method; calculated as $AUC_{last} + \frac{C_{last}}{\lambda_z}$ where C_{last} is the estimated concentration of the last quantifiable time point. (initial assessment)
$AUC_{0-\infty}/D$	Dose-normalized $AUC_{0-\infty}$ (initial assessment)
AUC_{0-96hr}	Area under the concentration versus time curve from 0 to 96 hours using linear Trapezoidal Linear/Log interpolation calculation method; if the sample at nominal time of 96 hours is missing, the activity at 96 hours will be interpolated or extrapolated using the last quantifiable activity and the terminal rate constant λ_z.(initial assessment)
AUC_{0-96hr}/D	Dose normalized AUC_{0-96hr} (initial assessment)
AUC_{tau}	Area under the concentration versus time curve over a dosing interval. (end of study assessment)
AUC_{tau}/D	Dose normalized AUC_{tau} (end of study assessment)
CL	Apparent total body clearance of the drug from blood, calculated as $\frac{\text{Dose(IU/kg)}}{AUC_{0-\infty}}$. (initial assessment)
C_{max}	Maximum observed concentration in a concentration-time profile after a single dose; obtained directly from the concentration-time data. (initial assessment)
C_{max}/D	Dose-normalized C_{max} (initial assessment)
$C_{max,ss}$	Maximum observed concentration at steady state. (end of study assessment)

$C_{max,ss}/D$	Dose-normalized $C_{max,ss}$ (end of study assessment)
$C_{min,ss}$	Minimum observed concentration at steady state. (end of study assessment)
$C_{min,ss}/D$	Dose-normalized $C_{min,ss}$ (end of study assessment)
IR at C_{max}	Incremental recovery, calculated as $\frac{C_{max}-C_{pre\text{-}infusion}}{Dose\ (IU/kg)}$ where C_{max} is the observed maximum concentration before correcting for pre-infusion values. (initial assessment)
IR at $C_{max,ss}$	Incremental recovery, calculated as $\frac{C_{max,ss}-C_{pre\text{-}infusion}}{Dose\ (IU/kg)}$ where $C_{max,ss}$ is the observed maximum concentration t steady state before correcting for pre-infusion values. (end of study assessment)
MRT	Mean residence time; calculated as $\frac{AUMC_{0-\infty}}{AUC_{0-\infty}} - \frac{TI}{2}$ where TI is the time duration of infusion, where $AUMC$ is the area under the first movement curve. (initial assessment)
$t_{\frac{1}{2}}$	Apparent terminal half-life; calculated as $\frac{\ln 2}{\lambda_z}$. (initial assessment)
t_{max}	Time to reach the C_{max} concentration after a single dose. (initial assessment)
$t_{max,ss}$	Time to reach the $C_{max,ss}$ concentration at steady state (end of study assessment)
V_{ss}	Apparent volume of distribution at steady state, calculated by $MRT \times CL$. (initial assessment)

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

Lambda z (λ_z)	Terminal elimination rate constant
Lambda z (λ_z) Interval	The time interval of the log-linear regression to determine λ_z.
Number of Points in Lambda z (λ_z)	Number of data points included in the log-linear regression analysis to determine λ_z.
$R_{sq_{adjusted}}$	Goodness-of-fit statistic for calculation of λ_z (coefficient of determination).
$\%AUC_{ex}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation.

For FVIII:C, only C_{max}, t_{max}, AUC_{0-96hr}, C_{max}/D, and AUC_{0-96hr}/D for initial assessment, as well as $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, AUC_{tau}, $C_{max,ss}/D$, $C_{min,ss}/D$, and AUC_{tau}/D for end of study assessment, will be calculated, if possible. Other PK parameters may be added at the discretion of the pharmacokineticist.

PK parameters for Cohort 1 to 4 subjects will be summarized using descriptive statistics by assessments (initial and end of study). Descriptive statistics for PK parameters will include n, mean, SD, geometric mean, % geometric CV, 95% CIs for both arithmetic and geometric means, first quartile (Q1), third quartile (Q3), minimum, median, and maximum, except that t_{max} will be reported with n, minimum, median, and maximum only.

Incremental recovery at visits without serial PK assessments will be calculated at each visit as $\frac{C_{post-dose}-C_{pre\text{-}infusion}}{Dose\ (IU/kg)}$, where $C_{post\text{-}dose}$ is the measured 30 minute post-dose concentration (without pre-infusion correction) and $C_{pre\text{-}infusion}$ is the measured pre-infusion concentration for the respective visit.

IR 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 prophylaxis treatment. Additionally, the pre-infusion concentrations will be summarized by visit for the initial 12 months of the prophylaxis treatment for the safety analysis set. Plots of arithmetic

mean IR for VWF:RCo, VWF:Ag, VWF:CB and arithmetic mean predose for FVIII activity (±SD, as appropriate) by visit will be presented on linear scale.

9. OTHER ANALYSES

9.1 Health-related Quality of Life Analyses

Analysis on HRQoL data will be performed descriptively on the FAS by VWD type, cohort and age group (where applicable). Data at Prophylaxis Initiation, Baseline, Month 6, Month 12 and End of Study will be summarized for tables of observed values while all data will be included in listings. If change from baseline tables are presented they will summarize Month 6, Month 12 and End of Study.

9.1.1 EQ-5D

Each question in the EQ-5D (3L, Y and parent-proxy) questionnaires will be presented as observed (by timepoint) and listed. The 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. 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 ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The VAS self-assessment is collected as part of the EQ-5D and will also be presented as observed and the change from baseline. Summaries will be presented by VWD type, cohort, and age group. A separate listing will be presented for the subjects that incorrectly received the 5 Level version of the EQ-5D.

9.1.2 SF-36

The SF-36 is a validated, generic HRQoL instrument measuring the following scales:

- Physical functioning
- Role limitations due to physical health
- Role limitations due to emotional problems
- Energy/fatigue
- Emotional wellbeing
- Social functioning
- Pain
- General health
- Physical component score

- Mental component score

Each of the 36 questions will be assigned to a specific scale and score based on the answers provided as set out in Section 15.1.1.

After scores have been assigned for each individual question, scores for scales will be calculated as set out in Table 2.

Table 2 SF-36 Scoring for Scales

Scale	Items to Sum (scores as assigned in Table 3)	Lowest and Highest Possible Score	Possible Raw Score Range
Physical Functioning (PF)	3a + 3b + 3c + 3d + 3e + 3f + 3g + 3h + 3i + 3j	10, 30	20
Role Physical (RP)	4a + 4b + 4c + 4d	4, 20	16
Bodily Pain (BP)	7 + 8	2, 12	10
General Health (GH)	1 + 11a + 11b + 11c + 11d	5, 25	20
Vitality (VT)	9a + 9e + 9g + 9i	4, 20	16
Social Functioning (SF)	6 + 10	2, 10	8
Role-Emotional (RE)	5a + 5b + 5c	3, 15	12
Mental Health (MH)	9b + 9c + 9d+ 9f + 9h	5, 25	20

The score for each scale will then be transformed to a 0 – 100 range using the following formula:

$$Transformed\ Scale = \frac{[(Actual\ Raw\ Score - Lowest\ Possible\ Raw\ Score)]}{Possible\ Raw\ Score\ Range} \times 100$$

A z-score standardization of the SF36 transformed scale scores will be determined as follows:

- $PF_z = \frac{PF - 83.29094}{23.75883}$
- $RP_z = \frac{RP - 82.50964}{25.52028}$

- $BP_z = \frac{BP - 71.32527}{23.66224}$
- $GH_z = \frac{GH - 70.84570}{20.97821}$
- $VT_z = \frac{VT - 58.31411}{20.01923}$
- $SF_z = \frac{SF - 84.30250}{22.91921}$
- $RE_z = \frac{RE - 87.39733}{21.43778}$
- $MH_z = \frac{MH - 74.98685}{17.75604}$

After the z-scores have been determined the z-scores will be used to determine norm-based scores that will be presented in listings and summaries. The norm-based score will be determined as:

$$XX_N = 50 + (XX_z \times 10)$$

where XX represents the difference scales (PF, RP, BP, GH, VT, SF, RE and MH).

The raw aggregate summary scores for the physical and mental components will be determined as follows:

- $AGG_{Phys} = (PF_z \times 0.42402) + (RP_z \times 0.35119) + (BP_z \times 0.31754) + (GH_z \times 0.24954) + (VT_z \times 0.02877) + \big(SF_z \times (-0.00753)\big) + \big(RE_z \times (-0.19206)\big) + \big(MH_z \times (-0.22069)\big)$
- $AGG_{Ment} = \big(PF_z \times (-0.22999)\big) + \big(RP_z \times (-0.12329)\big) + \big(BP_z \times (-0.09731)\big) + \big(GH_z \times (-0.01571)\big) + (VT_z \times 0.23534) + (SF_z \times 0.26876) + (RE_z \times 0.43407) + (MH_z \times 0.48581)$

The normalized aggregate scores that will be presented in listings and summaries will be determined as:

$$YY_N = 50 + (AGG_{YY} * 10)$$

where YY is either the physical component score or mental component score.

Any scale with less than half of the questions answered will have no score calculated. For scales with any questions not answered, but with more than half of the questions answered, the raw scale will be adjusted in terms of the lowest and highest possible score, including the possible raw range. All other scores will be affected by this change in raw

score. As an example, say question 3a is not answered, then the lowest score for physical functioning will change from 10 to 9, the highest score will change from 30 to 27 and the possible raw range from 20 to 18. The new values will be used in determining the raw score for physical functioning.

9.1.3 V-WIQ

The V-WIQ is a disease-specific instrument that assesses the physical and emotional well-being of adults with VWD.

The V-WIQ is comprised of 3 scales:

- Pain
- Impact of VWD
- Treatment related concerns

The pain scale consists of 1 item and no scoring are therefore conducted.

Each question in the questionnaire is assigned to a scale and domain and score as set out in Section15.1.2.

Domain scores are individually computed as the average of all the available responses, if and only if at least 50% of the questions are answered. If the condition is not met the domain score is not computed.

The impact of VWD scale score is computed as the average of the available responses, if and only if at least 50% of the responses from any given 4 domains (emotional, social, physical, and social functioning) are non-missing. If the condition is not met the scale is not computed.

Treatment-related concerns scale score is computed as the average of the available responses in the perceived efficacy, perceived safety and convenience domains, if and only if at least 50% of the domain responses are non-missing. If the condition is not met the scale score is not computed.

Higher scores represent worse quality of life while lower scores indicate better quality of life.

9.1.4 PedsQL

The PedsQL™ is a generic HRQoL designed specifically for the pediatric/adolescent population and records data for the following domains:

- Physical functioning
- Emotional functioning
- Social functioning
- School functioning

Each question of the PedsQL will be scored as follows:

- Never: 100
- Almost never: 75
- Sometimes: 50
- Often: 25
- Almost always: 0

The questionnaire consists of different questions based on the age of the subjects, namely for ages 2-4, 5-7 and 8-12 years. For younger children, there are parent-proxy versions for the age groups of 2-4 years and 5-7 years and a child version for the age group of 8-12 years. Scores for the categories of physical functioning, emotional functioning, social functioning and school functioning will be derived as the mean of the individual question scores of available data within each domain. Missing data will not be imputed. At least half of the questions in a domain needs to be answered for a score to be presented for that domain.

The psychosocial health summary score will be derived as the mean of the individual questions for the emotional, social and school functioning domains. The physical health summary score will be set equal to the physical functioning category score.

Higher scores represent better quality of life while lower scores indicate worse quality of life.

9.1.5 Treatment Satisfaction: TSQM-9

The TSQM-9 is comprised of 9 questions that provides scores on 3 scales:

- Effectiveness

- Convenience
- Global satisfaction

The scores of each scale will range from 0 to 100 with higher scores representing higher satisfaction with the treatment on that domain. The questionnaire does not contain a total score.

Scoring for each individual question is done as set out in Section 15.1.3.

The score for each scale is determined by calculating the difference between the sum of the responses in each scale and the lowest possible score, divided by the difference between the greatest and lowest possible scores. The result is then multiplied by 100. Only one item from a scale can be missing, otherwise the score for that scale will not be calculated. Examples are provided for each scale below:

Effectiveness Score: If none are missing, the effectiveness score would be:

$$Score = \frac{(sum\ of\ all\ 3\ responses) - 3}{18} \times 100.$$

If 1 response is missing, then the effectiveness score would be:

$$Score = \frac{(Sum\ of\ the\ 2\ non\text{-}missing\ responses) - 2}{12} \times 100.$$

Convenience Score: If none are missing, the convenience score would be:

$$Score = \frac{(sum\ of\ all\ 3\ responses) - 3}{18} \times 100.$$

If 1 response is missing, then the convenience score would be:

$$Score = \frac{(Sum\ of\ the\ 2\ non\text{-}missing\ responses) - 2}{12} \times 100.$$

Global Satisfaction Score: If none are missing, the global satisfaction score would be:

$$Score = \frac{(sum\ of\ all\ 3\ responses) - 3}{14} \times 100.$$

If either question 7 or 8 missing, then the global satisfaction score would be:

$$Score = \frac{(sum\ of\ the\ 2\ non\text{-}missing\ responses) - 2}{10} \times 100.$$

If question 9 is missing, then the global satisfaction score would be:

$$Score = \frac{(sum\ of\ the\ 2\ non\text{-}missing\ responses) - 2}{8} \times 100.$$

9.2 Healthcare Resource Utilization Analyses

Information on health resource use including number of primary care physician visits, hospital visits, emergency room visits, and days missed from school or work will be listed and summarized by age group, cohort and VWD type for the first 12 months and the entire study period.

Health resource utilization results will be annualized using the observation period in days as defined in Section 6.2.2.

9.3 COVID-19

Data collected in the database regarding missing visits related to COVID-19 will be summarized in a listing. Use *COVID-19 Impact missed visit* eCRF form.

10. INTERIM ANALYSIS AND AD HOC DATA MONITORING (REVIEW) COMMITTEE

An interim analysis to support the primary objective of the study will be performed after all subjects in prophylactic treatment cohorts have completed the 12-month visit. This interim analysis will include all the data available at the time of analysis and will be performed on a clean snapshot of the study database.

An interim analysis will also be performed at the time of database lock for parent study 071301 to support regulatory submission. This interim analysis will include subjects who rolled over from study 071301 only (cohorts 1, 2 and 6) and will include outputs related to primary and secondary efficacy and safety. Additional interim analyses may be performed as needed to support submissions to health authorities. The analysis will be limited to a subset of the data depending on the focus of the ad hoc or submission related requirements. Interim analyses will be performed on a clean snapshot of the study database.

A data monitoring committee (DMC) will be involved in providing oversight of subject safety in this late phase (phase 3b) clinical study, based on the criteria included in the DMC charter. The purpose of the DMC is to ensure the safety of the trial subjects, with a focus on pediatric population that is considered "vulnerable" (a. Guidance for Clinical Trial Sponsors-Establishment and Operation of Clinical Trial Data Monitoring Committees by the FDA, and b. Guideline on Data Monitoring Committees, EMEA/CHMP/EWP/5872/03 (2005) by the EMA/CHMP), by reviewing the study data as needed based on the criteria defined in the DMC charter. Further details regarding results that will be presented to the DMC will be documented in a separate document.

11. DATA HANDLING CONVENTIONS

11.1 General Data Reporting Conventions

Unless otherwise specified the default summary statistics for quantitative variables will be as follows:

- The number of subjects in each category (n)
- Mean
- SD
- Median
- 1st and 3rd quartiles
- Minimum
- Maximum

The above descriptive statistics will only be presented if there are at least 3 results available in a group. All statistics except median will be presented if only 2 results are available in a group while only n and mean will be presented if only 1 result is available in a group.

If the original data has N decimal places (as derived from the raw data) (i.e., decimal precision [N]) then the summary statistics will contain the following decimal places (with a maximum of 3 decimals):

- Minimum and maximum: N decimals
- Mean, median, and quartiles: N + 1 decimals
- Standard deviation: N + 2 decimals

For qualitative variables the number (n) and percentage (%) of subjects in each category will be the default summary presentation. Unless otherwise specified percentages will be calculated relative to the total number of subjects in the relevant analysis set with data available as described in the latest version of the Output Templates.

All values will be rounded using the SAS® function ROUND. All computed percentages will be presented using 1 decimal place, except for 100% which will be presented with no decimals.

The default significance level will be 5%; confidence intervals 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

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

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

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

11.2 Reference Start Date and Study Days

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

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

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

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

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

11.3 Study Periods

Where mentioned in the description of the specific analyses, the analyses will be conducted for different study periods. These study periods are:

- The first 12 months.
- The first 24 months.
- The entire study.

All periods will start from the Reference Start Date as described in Section 11.2.

The end date for the 12- and 24-month periods will be the Month 12 and Month 24 visits respectively.

Should a subject not have the Month 12 or Month 24 visit the end date will be determined from reference start date by adding 12 or 24 months respectively. Additionally, after the 12 or 24 months have been added another 2 weeks will be added to allow for the protocol specified window for these visits. This will allow for comparison with subjects that did have the visit.

Should a subject discontinue before having the Month 12 visit, the first 12 months period and the first 24 months period will end on the date of discontinuation. Should a subject discontinue after the Month 12 visit, but before the Month 24 visit, the first 12 months will be defined as described above. The first 24 months period will have the discontinuation date as the end date. For the interim analysis performed at the time of database lock for parent study 071301, subjects who have neither discontinued nor completed the Month 12 visit will have the data cut-off date as the end date.

Any result occurring before the end date of the first 12 months will be included in analyses for the first 12 months. Similarly, any result occurring before the end date of the first 24 months will be included in the analyses of the first 24 months.

For analyses on the entire study period, all data recorded in the eCRF will be used, without considering the timing of the results, unless otherwise specified in the description of the specific analyses.

11.4 Data from Parent Study

Historic data for subjects transitioning from either the 071301 or 071102 study will be transcribed from the parent study's database. The end of study results of the parent study should be used as Screening results for this current Continuation study if the assay is not repeated. The end of study results from the parent study will also be transcribed from the parent study's database. Data transcribed from the screening visit of the parent study includes demography, medical history, disease history, and genetic testing history. Data transcribed from the completion/termination visit of the parent study eCRF includes physical exam, vital signs, central laboratory, and ongoing adverse events and concomitant medications.

11.5 Definition of Baseline

Unless otherwise specified, baseline is defined as the last non-missing (scheduled or unscheduled) measurement obtained prior to the Reference Start Date as defined in Section 11.2. It is therefore possible that baseline data may be obtained from the parent study as described in Section 11.4. This definition of baseline will be applicable to safety, efficacy and HRQoL data.

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

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

11.6 Repeated or Unscheduled Assessments of Safety Parameters

In the case of retests or repeated assessments, the last available measurement for that visit will be used for by-visit summaries.

Unscheduled results will not be included in summaries.

All results (scheduled and unscheduled; original and repeated) will be presented in listings.

11.7 Handling of Missing, Unused, and Spurious Data

11.7.1 Missing Date Information for Prior or Concomitant Medications (Non-drug Therapies/Procedures)

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

11.7.1.1 Incomplete Start Date

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

11.7.1.1.1 Missing Day, Month and Year

- Start date assigned to date for first IP administration.

11.7.1.1.2 Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of IP, then the day and month of the date of the first dose of IP will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the date of the first dose of IP, then December 31 will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of the first dose of IP, then 01 January will be assigned to the missing fields.

11.7.1.1.3 Missing Month Only

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

11.7.1.1.4 Missing Day Only

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

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

11.7.1.2 Incomplete Stop Date

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

11.7.1.2.1 Missing Day, Month and Year

- No end date will be assumed, i.e., it will be assumed as ongoing.

11.7.1.2.2 Missing Day and Month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of IP, then the day and month of the date of the last dose of IP will be assigned to the missing fields.
- If the year of the incomplete stop date is before the year of the date of the last dose of IP, then 31 December will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the date of the last dose of IP, then 01 January will be assigned to the missing fields.

11.7.1.2.3 Missing Month Only

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

11.7.1.2.4 Missing Day Only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of IP, then the day of the date of the last dose of IP will be assigned to the missing day.
- If either the year is before the year of the date of the last dose of IP or if both years are the same, but the month is before the month of the date of the last dose of IP, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the last dose of investigational product or if both years are the same, but the month is after the month of the date of the last dose of IP, then the last day of the month will be assigned to the missing day.

11.7.2 Missing Date Information for Adverse Events

For AEs with partial start dates, non-missing date parts will be used to determine if the AE is treatment-emergent or not following the same rules as in Section 11.7.1.1. In addition, the eCRF also records timing relative to dose should date information of an AE be unknown, which will also be considered to determine if an AE is a TEAE. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to IP administration, e.g., AE start year and month are the same as the year and month of the first dose of IP or using the relative time to IP entered on the eCRF then the AE will be classified as treatment emergent.

AEs with completely missing start dates will be considered treatment-emergent and AEs with completely missing stop dates will be considered ongoing.

11.7.3 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of IP, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of IP, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries.

11.7.4 Missing Relationship to Investigational Product for Adverse Events

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

12. ANALYSIS SOFTWARE

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

13. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

The FAS was updated from "The full analysis set (FAS) will be composed of all enrolled subjects who received IP" to "The full analysis set (FAS) will consist of all subjects who satisfy all entry criteria and received any amount of IP".

The PKAS was updated from "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 one quantifiable post-dose measurement without any significant protocol deviations or events with potential to affect PK." to "The PK analysis set

(PKAS) will be composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post-dose measurement for pharmacokinetic and/or pharmacodynamic analysis".

For perioperative management of bleeding the protocol specifies it will be on the first 12 months of study treatment, except for the weight-adjusted dose, which will be for the entire study period. However, the data as noted in section 6.3.1 has been collected for surgeries throughout the study and will be summarized and listed as described in this SAP.

The duration of hospital stays is not collected directly on the healthcare resource utilization eCRF page and will not be summarized with other data from this eCRF page.

14. REFERENCES

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European Medicines Agency (EMA). (2006). Guideline on the Clinical Investigation of Human Plasma Derived von Willebrand Factor Products (CPMB/BPWG/220/02).

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15. APPENDICES

15.1 Questionnaire Scoring

15.1.1 SF-36

Table 3 SF-36 Scoring for Individual Questions

Question	Scale	Score
1. In general, would you say your health is:	General Health	Excellent: 5 Very Good: 4 Good: 3 Fair: 2 Poor: 1
2. Compared to one year ago, how would you rate your health in general now?	No Scale	Much better now than one year ago: 1 Somewhat better now than one year ago: 2 About the same as one year ago: 3 Somewhat worse now than one year ago: 4 Much worse now than one year ago: 5
3. The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?		
3a. Vigorous activities	Physical Functioning	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3b. Moderate activities	Physical Functioning	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3c. Lifting or carrying groceries	Physical Functioning	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3d. Climbing several flight of stairs	Physical Functioning	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3e. Climbing one flight of stairs	Physical Functioning	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3f. Bending, kneeling or stooping	Physical Functioning	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3g. Walking more than a mile	Physical Functioning	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3h. Walking several hundred yards	Physical Functioning	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3i. Walking one hundred yards	Physical Functioning	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3j. Bathing or dressing yourself	Physical Functioning	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?		
4a. Cut down on the amount of time you spent on work or other activities	Role-Physical	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
4b. Accomplished less than you would like	Role-Physical	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5

Question	Scale	Score
4c. Were limited in the kind of work or other activities	Role-Physical	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
4d. Had difficulty performing the work or other activities (for example, it took extra effort)	Role-Physical	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?		
5a. Cut down on the amount of time you spent on work or other activities.	Role-Emotional	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
5b. Accomplished less than you would like	Role-Emotional	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
5c Did work or other activities less carefully than usual	Role-Emotional	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?	Social Functioning	Not at all: 5 Slightly: 4 Moderately: 3 Quite a bit: 2 Extremely: 1
7. How much bodily pain have you had during the past 4 weeks?	Bodily Pain	None: 6 Very mild: 5.4 Mild: 4.2 Moderate: 3.1 Severe: 2.2 Very severe: 1
8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Bodily Pain	<u>If Question 7 Answered:</u> Not at all (and Question 7 = None): 6 Not at all (and Question 7 not None): 5 A little bit: 4 Moderately: 3 Quite a bit: 2 Extremely: 1 <u>If Question 7 Not Answered:</u> Not at all: 6 A little bit: 4.75 Moderately: 3.5 Quite a bit: 2.25 Extremely: 1
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...		
9a. Did you feel full of life?	Vitality	All of the time: 5 Most of the time: 4 Some of the time: 3 A little of the time: 2 None of the time: 1
9b. Have you been very nervous?	Mental Health	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5

Question	Scale	Score
9c. Have you felt so down in the dumps that nothing could cheer you up?	Mental Health	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
9d. Have you felt calm and peaceful?	Mental Health	All of the time: 5 Most of the time: 4 Some of the time: 3 A little of the time: 2 None of the time: 1
9e. Did you have a lot of energy?	Vitality	All of the time: 5 Most of the time: 4 Some of the time: 3 A little of the time: 2 None of the time: 1
9f. Have you felt downhearted and depressed?	Mental Health	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
9g. Did you feel worn out?	Vitality	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
9h. Have you been happy?	Mental Health	All of the time: 5 Most of the time: 4 Some of the time: 3 A little of the time: 2 None of the time: 1
9i. Did you feel tired?	Vitality	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
10. During the past 4 weeks how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives etc.)?	Social Functioning	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
11. How true or false is each of the following statements for you?		
11a. I seem to get sick a little easier than other people	General Health	Definitely true: 1 Mostly true: 2 Don't know: 3 Mostly false: 4 Definitely false: 5
11b. I am as healthy as anybody I know	General Health	Definitely true: 5 Mostly true: 4 Don't know: 3 Mostly false: 2 Definitely false: 1
11c. I expect my health to get worse	General Health	Definitely true: 1 Mostly true: 2 Don't know: 3 Mostly false: 4 Definitely false: 5
11d. My health is excellent	General Health	Definitely true: 5 Mostly true: 4 Don't know: 3 Mostly false: 2 Definitely false: 1

15.1.2 V-WIQ

Table 4 V-WIQ Domains, Scales and Scoring

Question (Over the past 7 days, …)	Domain	Scale	Score
1) How severe was your physical pain at its worst because of your VWD?	Pain	Pain	NA
2) How often were you in a depressed mood because of your VWD?	Emotional function	Impact of VWD	Method 1
3) How often did you feel embarrassed because of your VWD?			Method 1
4) How often did you feel worried because of your VWD?			Method 1
5) How much did your VWD affect your relationships with family?	Social function		Method 2
6) How much did your VWD affect your relationships with friends?			Method 2
7) How much did your VWD limit you from participating in social activities with people who are familiar with your condition?			Method 2
8) How much did your VWD limit you from participating in social activities from people who are not familiar with your condition?			Method 2
9) How often did you have to cancel planned activities because of your VWD?			Method 1
10) How much difficulty did you have doing strenuous activities because of your VWD?	Physical function		Method 3
11) How often did you miss work or school because of your VWD?	Work/school function		Method 1
12) How much did your VWD affect your performance at work or school?			Method 2
13) How much did your VWD affect your relationships at work or school?			Method 2
14) How worried were you that your treatment was not working?	Perceived efficacy	Treatment-related concerns	Method 2
15) How worried were you about the safety of your treatment?	Perceived safety		Method 2
16) How would you rate the convenience of your treatment?	Convenience		Method 4

Table 5 V-WIQ Method 1 Scoring

Response	Score
All of the time	100
Most of the time	75
Some of the time	50
A little of the time	25
None of the time	0

Table 6 V-WIQ Method 2 Scoring

Response	Score
Not at all	0
A little bit	25
Moderately	50
Quite a bit	75
A lot	100

Table 7 V-WIQ Method 3 Scoring

Response	Score
No difficulty	0
A little difficulty	25
Moderate difficulty	50
Quite a bit of difficulty	75
Extreme difficulty	100

Table 8 V-WIQ Method 4 Scoring

Response	Score
Very convenient	0
Somewhat convenient	25
Neither convenient nor inconvenient	50
Somewhat inconvenient	75
Very inconvenient	100

15.1.3 TSQM-9

Table 9 TSQM-9 Scoring

Scale	Question	Response	Score
Effectiveness	1) How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?	Extremely dissatisfied	1
		Very dissatisfied	2
		Dissatisfied	3
		Somewhat satisfied	4
		Satisfied	5
		Very satisfied	6
		Extremely satisfied	7
	2) How satisfied or dissatisfied are you with the way the medication relieves your symptoms?	Extremely dissatisfied	1
		Very dissatisfied	2
		Dissatisfied	3
		Somewhat satisfied	4
		Satisfied	5
		Very satisfied	6
		Extremely satisfied	7
	3) How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?	Extremely dissatisfied	1
		Very dissatisfied	2
		Dissatisfied	3
		Somewhat satisfied	4
		Satisfied	5
		Very satisfied	6
		Extremely satisfied	7
Convenience	4) How easy or difficult is it to use the medication in its current form?	Extremely difficult	1
		Very difficult	2
		Difficult	3
		Somewhat easy	4
		Easy	5
		Very Easy	6
		Extremely Easy	7
	5) How easy or difficult is it to plan when you will use the medication each time?	Extremely difficult	1
		Very difficult	2
		Difficult	3
		Somewhat easy	4
		Easy	5
		Very Easy	6
		Extremely Easy	7
	6) How convenient or inconvenient is it to	Extremely inconvenient	1

Scale	Question	Response	Score
	take the medication as instructed?	Very inconvenient	2
		Inconvenient	3
		Somewhat convenient	4
		Convenient	5
		Very convenient	6
		Extremely convenient	7
Global Satisfaction	7) Overall, how confident are you that taking this medication is a good thing for you?	Not at all confident	1
		A little confident	2
		Somewhat confident	3
		Very confident	4
		Extremely confident	5
	8) How certain are you that the good things about your medication outweigh the bad things?	Not at all certain	1
		A little certain	2
		Somewhat certain	3
		Very certain	4
		Extremely certain	5
	9) Taking all things into account, how satisfied or dissatisfied are you with this medication?	Extremely dissatisfied	1
		Very dissatisfied	2
		Dissatisfied	3
		Somewhat satisfied	4
		Satisfied	5
		Very satisfied	6
		Extremely satisfied	7

15.2 SAS code

15.2.1 Wald Confidence Intervals

```
PROC CATMOD DATA = <ds>;
    RESPONSE 1 0 0 0, 0 1 0 0;
    WEIGHT <count>;
    MODEL <category> = /clparm;
RUN;
```

where <ds> refers to the input dataset, <count> the number of subjects in the specific category and <category> the particular category in question.

The response statement includes 0's and 1's to the amount of the number of categories included in the analysis. In the above code example, we have 4 different categories. To get the estimate for the first category the "1 0 0 0" needs to be included. Similarly, to get the estimates for second category the "0 1 0 0" needs to be included. It is important to ensure that the input dataset is sorted in the correct order from lowest category to highest category before running the above code.

15.2.2 Clopper-Pearson

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

where <ds> refers to the input dataset, <count> the number of subjects with the specific category and <result> the actual result, i.e., "Yes" vs. "No".

15.2.3 Kaplan-Meier

```
PROC LIFETEST DATA=<ds> ALPHA=0.05 PLOTS=
SURIVAL(FAILURE);
     STRATA <regimen>;
     TIME <time> * <censor> (1);
RUN;
```

where <ds> refers to the input dataset, <regimen> the prophylactic regimen, <time> the time to first bleed (or censoring if applicable) and <censor> the flag for records being censored (with censored records flagged as 1).

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