Statistical Analysis Plan (SAP)

Sponsor:	Octapharma Pharmazeutika Produktionsges.m.b.H.
Study Title:	Clinical Study to Investigate the Efficacy, Pharmacokinetics, Immunogenicity and Safety of *wilate* in Severe von Willebrand Disease Patients under the Age of 6 Years
Protocol Version/Date:	Version 03; 2022-12-05 Supplemental Amendment 4.0, 2022-12-05 (supplementing Protocol V03) Protocol Amendment 5.0, 2023-07-20 (Czechia only, based on V03)
SAP Version/Date:	Version 2.0; 2025-02-12
Supersedes SAP Version:	Version 1.0; 2021-01-15
Appendices (external documents):	1. List of Tables, Listing, Figures (TLFs)

Approval

The Trial Statistician hereby confirms that the SAP was prepared in conformance with the procedures and principles set forth in the indicated protocol version and all established relevant guidelines.

Name **Affiliation, Function**	**Signature:**	**Date:**
[redacted] Ergomed, Trial Statistician	electronically signed	

By signing hereafter, I confirm that this Statistical Analysis Plan adequately describes the statistical analyses to be performed in the context of this study.

Name **Affiliation, Function**	**Signature:**	**Date:**
[redacted], Clinical R&D Haematology Octapharma Pharmazeutika Produktionsges.m.b.H	electronically signed	

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[redacted] Octapharma AG	electronically signed	

Revision history

SAP Version	Version date	Reason(s) for change
1.0	2021-01-15	Not applicable. Initial version.
2.0	2025-02-12	• Updating list of abbreviations • Adding subjects with major PK over- or underdosing to individual protocol deviation list (section 2.3) • Adding details to definitions of analysis populations in sections 3.4 (exclude from SURG if no IMP prior to start of surgery or intraoperatively), 3.5 (exclusion of invalid values from PK analysis) and 3.7 (explain valid primary endpoint) • Adding PK-PP set (section 3.6) • Adding analysis subgroups VWD type and sex and rephrasing of multimer analysis description (section 3.8) • Update handling of values below LLOQ and specifications for number of digits (section 4) • Specifying handling of re-enrolled subject 33-31-01/33-31-02 in analysis (section 4) and robustness analysis (section 4.7.1) • Handling of commercial wilate in efficacy analysis (section 4.7.2) • Adding details to exploratory efficacy endpoint VWF multimer analysis (section 4.7.3) • Adding additional annualized bleeding rate (ABR) analyses for treated BEs as well as for prior BEs • Adding details to baseline definition (section 4.1.1) • Update for surgery analysis considering number of observations (section 4.7.2) • Update formulas for derived variables (section 6.1) • Update of IMP potency information and add formulas for calculation of prior ABR analyses (section 6.1)

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LIST OF ABBREVIATIONS

Abbreviation	Description
ABR	Annualised Bleeding Rate
AE	Adverse Event
Ag	Antigen
ALT	Alanine Aminotransferase
AST	Aspartate Transaminase
AUC	Area under the Curve
BE	Bleeding Episode
BW	Body Weight
CI	Confidence Interval
CRO	Contract Research Organisation
DRM	Database Review Meeting
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
FVIII	Factor VIII
GCP	Good Clinical Practice
HJHS	Haemophilia Joint Health Score
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention-To-Treat
IU	International Units
IVR	In Vivo Recovery
LLOQ	Lower Limit of Quantitation
MedDRA	Medical Dictionary for Regulatory Activities
OS	One-Stage (Assay)
PP	Per Protocol
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SURG	Surgery (Population)

Abbreviation	Description
TABR	Total Annualised Bleeding Rate
TEAE	Treatment-Emergent Adverse Event
VWD	Von Willebrand Disease
VWF	Von Willebrand Factor
VWF:Ac	Von Willebrand Factor Activity
VWF:RCo	Von Willebrand Ristocetin Cofactor Activity

1 STUDY INFORMATION

The purpose of this study is to obtain additional data on the efficacy, PK, immunogenicity, and safety of *wilate* in paediatric patients below the age of 6 years with severe VWD undergoing regular prophylaxis.

Other studies have demonstrated a beneficial effect of prophylaxis with VWF treatment in patients with severe VWD, including paediatric patients. These studies reported reduced mucosal and joint bleeding rates, decreased median ABR, a reduced incidence of major bleeds, and good tolerability.

1.1 Primary objective

The primary objective of this study is to determine the efficacy of *wilate* in the prophylactic treatment of up to 12 paediatric patients (eight evaluable) with severe VWD (defined as von Willebrand ristocetin cofactor activity [VWF:RCo] < 20%) under the age of 6 years, for a period of 12 months.

1.2 Secondary objectives

The secondary objectives of this study are to:

- Determine the pharmacokinetics (PK) of *wilate* for VWF:Ac (VWF:RCo) and FVIII:C (one-stage [OS])
- Determine incremental in-vivo recovery (IVR) of *wilate* over time
- Evaluate the rate of traumatic and spontaneous breakthrough bleeds under prophylactic treatment, including the corresponding treatment efficacy
- Assess the treatment response in minor and major bleeds and surgeries
- Determine *wilate* consumption data for prophylactic treatment, on-demand treatment, and surgeries
- Investigate the immunogenic potential of *wilate* by screening for VWF and FVIII inhibitors
- Investigate the thrombogenic potential of wilate
- Assess the patients' joint status with the Haemophilia Joint Health Score (HJHS)
- Assess the safety and tolerability of *wilate*

1.3 Exploratory Objectives

The exploratory objective of this study is to investigate the VWF multimer composition in the hereditary type 3 VWD paediatric patient group.

1.4 Study design

This is an open-label, prospective, non-controlled, international, multi-centre phase 3 study investigating the efficacy, pharmacokinetics, immunogenicity, and safety of *wilate*

in paediatric patients below the age of 6 years at the time of screening with severe VWD (defined as VWF:RCo < 20%, regardless of prior treatment) undergoing regular prophylaxis.

Overall, 12 patients (8 evaluable) suffering from severe VWD will be enrolled by up to 15 study sites worldwide. At least four of these patients should be suffering from hereditary type 3 VWD. The remaining patients can be diagnosed with severe type 2 (except 2N) or severe type 1 VWD.

Of the 12 patients, at least 8 patients should be evaluable for the primary endpoint.

The planned prophylactic treatment duration per patient is 12 months (+2 weeks).

Patients will participate in the following visits: Screening Visit, Baseline PK Visit, 1, 2, 3-Month, 6-Month, and 9-Month Visits, and a Study Completion (12-Month) Visit. Moreover, "Compliance Calls" will be performed 5–7 weeks after each quarterly visit.

Parents will receive product for home treatment and will be instructed on proper storage and administration. Involvement of a physician or a study nurse will be documented.

1.5 Planned sample size

No formal sample size calculation was performed for the study. The sample size of up to 12 patients, including at least 4 patients with VWD type 3, is based on a communication with the FDA and on EU guideline CPMP/BPWG/220/02 calling for a trial in at least eight children with VWD under the age of six years, three of whom should have type 3 VWD. A sample of 12 patients was finally selected to accommodate for drop-outs.

2 GENERAL INFORMATION

2.1 Background details

All study data will be transferred to a SAS database (version 9.4 or later) for statistical analysis purposes. Data will be imported from a Data Capture System via validated SAS programs. The SAP will be finalized before database lock after agreement with the Sponsor on subject disposition and coding.

2.2 Deviations from the trial protocol with impact on statistical analyses

The following general deviations from the protocol will be considered as being important for the statistical analysis:

- Patients who entered the study although they did not satisfy the eligibility criteria.
- Patients who received the wrong treatment or incorrect dose.
- Patients with substantial deviations from the timing foreseen for the prophylactic treatment regimen.
- Patients who received forbidden concomitant medication.

2.3 Individual protocol deviations

Apart from violations of in- or exclusion criteria the table below lists conditions that may affect the evaluation of subject data and the proposed actions:

Condition	Decision Rule
Subjects not exposed to *wilate*	Exclude from PP, FAS, SAF
Subjects with substantial deviations from the prophylactic treatment regimen, as agreed during the DRM	Exclude from PP
Subjects without evaluable PK-samples	Exclude from PK
Subjects with major PK over- or underdosing	Exclude from PK-PP

A detailed review of all documented and derived deviations from protocol will be part of a Data Review Meeting (DRM) before database lock. During this DRM the impact of protocol deviations on the analysis will be assessed and the conclusions recorded.

A complete listing of documented and derived protocol deviations and the judgment for assessment of subject disposition will be signed before database lock. A description of protocol violations that led to exclusion from any analysis sets will be included in the table part of the CSR.

3 ANALYSIS POPULATIONS

In general, the disposition of subjects will be displayed for the subject populations defined below.

Membership of subjects will be decided upon in a DRM with the Sponsor before database lock. The proper flags for analysis sets exclusion (e.g., exclusion from PP set), will be included in the analysis datasets. The protocol deviation list should be finalized before database lock.

- The analysis of safety will be based on the SAF set.
- The evaluation of the primary endpoint will be performed on the FAS (ITT analysis) and on the PP set (PP analysis).
- For secondary and exploratory endpoints, ITT and PP analyses will be carried out, unless these analysis sets differ by no more than 1 patient.
- Analysis of the efficacy and safety of *wilate* in surgeries will be based on the SURG set.
- Analysis of the PK properties of *wilate* will be based on the PK set.

3.1 Screening Failures

Subjects who signed the Informed Consent Document but did not receive IMP will be considered screening failures.

3.2 Safety Analysis Set

The Safety Set (SAF) will include all patients who received at least one dose of IMP.

3.3 Full Analysis Set

The Full Analysis Set (FAS), defined according to the intention-to-treat (ITT) principle, will include all enrolled patients who received at least one dose of IMP after the completion of the PK assessment.

3.4 Surgery Analysis Set

The Surgery Analysis Set (SURG) will be a subset of the FAS, containing all patients who underwent a surgical procedure during their prophylactic treatment phase and were treated with IMP prior to the start of surgery or intraoperatively.

3.5 Pharmacokinetic (PK) Set

The Pharmacokinetic Set will be a subset of the SAF containing all patients for whom a valid PK profile could be obtained from the PK visit. Invalid samples/PK profiles (e.g. hemolyzed samples, incomplete PK) as well as patients with inhibitors at the PK visit will be excluded from the PK-analysis during DRM.

3.6 Pharmacokinetic Per-protocol Set

The Pharmacokinetic Per-Protocol set (PKPP) will be a subset of the PK Set excluding subjects with a major protocol deviation regarding PK dosing.

3.7 Per-protocol Set

The Per-Protocol Set (PP) is a subset of subjects in the FAS.

It includes all subjects who were treated according to the protocol without any important protocol deviations (as finally defined during DRM) and had a valid primary endpoint (valid documentation of BEs during 12 Months (- 4 weeks) of prophylactic treatment).

3.8 Subgroup analyses

As mentioned in section 1.3 of the SAP, an additional multimer analysis using low- and high-resolution electrophoresis gels will be performed only in the subgroup of patients with hereditary type 3 VWD with ≥14.5 kg body weight. The multimer composition will be investigated over time for PK sampling time points15 minutes, and 24 hours after IMP injection (for details see section 4.7.3).

The analysis of demographics and all efficacy analyses (except for the VWF type 3 subgroup) will be stratified by the following subgroups:

- VWD type (‘severe type 1’, ‘type 2’ and ‘type 3’)
- Sex (‘Female’, ‘Male’)

The safety analysis will be stratified by sex.

4 STATISTICAL ANALYSES

All statistical analyses will be performed using the SAS® software (Version 9.4 or later).

Descriptive statistics will be given for the analysis set relevant for the different endpoints. For baseline and basic variables, they will also be given for the safety analysis set.

If not stated otherwise the following standard types of descriptive analyses will be presented:

– Descriptive statistics for continuous data

N, mean, SD, min, lower quartile, median, upper quartile and max will be presented. These descriptive statistics will be determined for measured values and optionally for differences to baseline.

– Descriptive statistics for categorical data

Absolute frequencies (N) will be presented with 0, relative frequencies (%) with at least 1 decimal. Percentage bases (denominators) will be identified in the table title or footnote (i.e. all subjects at risk, all non-missing cases, all cases). For changes from baseline, shift tables will be generated (prophylactic treatment regimen, vital signs, safety laboratory)

– Inferential statistics

Unless otherwise stated, all statistical tests will be performed two-sided and at a type I error probability of α=0.05.

Unless otherwise stated, all confidence intervals (CIs) will be derived two-sided and at a confidence probability of 1-α=0.95.

All p-values will be rounded to 4 decimals ($p<0.0001$ will be displayed if the p-values are less than 0.0001). Unless otherwise specified, statistical significance will be declared if the rounded p-value will be less than 0.05.

- PK/IVR analysis

For presentation of pharmacokinetic concentrations/activities for FVIII and VWF in tables and figures and for PK/IVR analysis, values below the lower limit of quantitation (LLOQ) will be set to ½ LLOQ. In case that more than half of the values per timepoint are below LLOQ descriptive statistics (except maximum) will not be calculated.

For PK analysis plasma concentrations/activities and PK parameters will be summarized using descriptive statistics (number of values (n) or number of subjects (N), geometric mean, geometric coefficient variation (CV%), arithmetic mean, standard deviation (SD), median, minimum and maximum). The geometric mean is calculated as the exponential of the arithmetic mean calculated from data on a log scale. The CV% is calculated as $CV\% = 100 \cdot \sqrt{\exp(s2) - 1}$ where s is the standard deviation of the data on a log scale.

- Figures

For graphical presentation of IVR, arithmetic mean (+/- SD) IVR over-time will be plotted.

For graphical presentation of PK, individual subject PK-profiles will be plotted in linear and semi logarithmic scale. Furthermore, arithmetic means (+/- SD) of pre-dose adjusted FVIII and VWF activities will be plotted in linear scale, and geometric means (+/- SD) in linear as well as in semi logarithmic scale.

– Listings

All recorded data will be listed by subject. Identification variables will always be the unique subject ID. Other IDs, e.g. Adverse event ID, will be added as required.

Derived data will be stored in special analysis data sets and will be calculated as outlined in section 6.1.

Handling of subject 33-31-01/33-31-02 in efficacy and safety analysis

Patient 33-31-01 left Ukraine after ~2 months of prophylactic treatment and thus discontinued the study prematurely but was re-enrolled (ID 33-31-02) after 189 days, provided that the regular 12-Month prophylactic treatment phase was restarted. Both, the initial study phase (first screening until premature study termination), as well as the regular study phase (second screening until regular completion) will be included in the safety and efficacy analysis.

For the primary endpoint a robustness analysis will be performed which is based on the regular 12-months prophylactic phase only (see section 4.7.1).

4.1 Conventions

4.1.1 Baseline definition

Assessments before first exposure to IMP at PK visit or at screening visit (in case the corresponding assessment is not scheduled at PK visit) are considered as baseline. In case that no measurements are available at either of these visit (for safety laboratory, physical examination and Haemophilia joint health score before the first IMP infusion), the proximal value before the screening visit can be used as baseline.

For patient 33-31-01/02, assessments at initial screening/initial PK visit (initial study phase before re-enrolment) are considered as baseline (see also “Handling of subject 33-31-01/33-31-02” in section 4).

4.1.2 Missing data

In general, missing data will not be imputed. Calculations pertaining to the derivation of the TABR will be based on documented time periods only.

Only in case of missing body weight will the last available body weight measurement be used for calculating the dose per kg body weight (last observation carried forward, LOCF).

4.1.3 Pooling of centres

All tables will be presented in total over all participating countries and centres. The distribution of number of subjects per country and centre will be presented in the disposition section of the report. No pooling of centres will be performed.

For additional standards and conventions applied in the generation of statistical outputs please refer to section 8.

4.2 Demographic and other background data

4.2.1 Basic description

The disposition of subjects (cf. Section 3) will be tabulated for the entire population. Details on protocol deviations will be listed.

Discontinued subjects will be described by frequency distributions including the reasons and in individual listings.

Demographic data (age, weight, height, BMI, race, ethnic group) will be summarized in tables and presented for the SAF and FAS population. Other baseline or background data, e.g. disease-specific information, will comprise descriptive tables for the SAF and FAS population for the following variables:

- Blood group (from medical records or obtained anytime during the study)
- VWF:Ag, VWF:Ac levels from medical records
- FVIII inhibitor level
- Vital Signs (blood pressure, heart rate, body temperature, and respiratory rate) at screening
- Physical examination (normal/abnormal) at screening
- Haemophilia joint health score (HJHS) at screening

The following background data will only be listed:

- Medical history
- Concomitant Medication

4.2.2 Homogeneity tests

Not applicable

4.3 IMP exposure, compliance

For all IVR and PK Assessments, IMP will be administered at the study site, with compliance under the control of the treating investigator.

Adherence with the treatment regimen will be assessed throughout the study. Any change of the prophylactic dose as determined by the responsible treating investigator during the Baseline Visit will be documented in the patient records and eCRF, including start and end dates of each dose and the reason for dose change.

Parents should be contacted via telephone every 5–7 weeks between the later quarterly visits. All IMP treatment details will be listed.

4.4 Medical history, physical examination

Data on medical history will be listed. Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Codes will be reviewed by a Medical Expert and approved by the sponsor before data base lock.

4.5 Prior and concomitant medication

Any relevant medication taken at time of screening and all new medications taken by the subject during the study period are defined as 'Concomitant'. Any changes of medications during the study period will also be recorded.

All details of concomitant medications will be listed including the route, dose, frequency, start and stop date and indication.

Medications will be coded using the WHO Drug Global thesaurus in the version current at the time of study start. Coding will be performed by the CRO and agreed upon with the sponsor before data base lock. (cf. DMP). For concomitant medications tables will show the frequencies of subjects by WHO Drug Global preferred term.

Prior medication will be listed only.

4.6 Concomitant non-pharmacological measures

Not applicable

4.7 Efficacy

The analysis of the efficacy of prophylactic treatment with IMP will be based on the FAS and the PP set unless these analysis sets differ by not more than one patient. Otherwise, the analysis will be presented only for the FAS.

Primarily, all obtained data on treatment characteristics (IMP dosages, frequencies, total consumption), VWF:Ac and FVIII:C incremental IVR of IMP over time and BEs (duration, frequency, efficacy assessment) will be described using summary statistics.

4.7.1 Primary endpoint

The primary endpoint of this study is to determine the total annualised bleeding rate (TABR) during prophylactic treatment with IMP.

The haemostatic efficacy of IMP will be assessed by evaluating TABR over all types of VWD.

The frequency and severity of BEs and the total, traumatic and spontaneous ABR will be calculated from patients' dosing and treatment frequency in different VWD types. Efficacy of prophylactic treatment with IMP will be statistically evaluated by analysing the primary endpoint.

The TABR will be calculated as the total number of spontaneous bleeds, traumatic bleeds, and other bleeds occurring in the time period between first prophylactic dose of IMP and the Study Completion Visit, divided by the duration (in years) between first prophylactic dose of IMP and the Study Completion Visit. Bleeding episodes occurring within surgery periods will be excluded from the calculation of TABR.

In addition to the estimates of the TABR exploratory 95% CIs will be calculated from a Poisson regression model.

Robustness analyses

For the analysis of efficacy endpoint (ABR), two prophylactic treatment phases will be combined for the special case of subject 33-31-01/33-31-02, i.e. the initial 2-month prophylactic treatment phase and the regular 12-month prophylactic treatment phase. Since the longer total duration of the combined prophylactic treatment phase and the study interruption of 189 days might have an influence on the ABR, the robustness of the ABR analysis will be investigated by additionally presenting the ABR analysis only for the regular 12-months prophylactic phase (excluding the initial phase). The robustness analysis will be performed for the FAS and additionally for the PP-population including subject 33-31-02 to obtain the ABRs for a per-protocol 12-months prophylactic treatment period.

4.7.2 Secondary endpoints

The secondary endpoints of this study are to determine:

- Baseline PK profile characteristics of VWF:Ac (VWF:RCo) and FVIII:C (OS) based on blood samples taken pre-dose (baseline), 30 minutes, 3, 9, 24, 48 and 72 hours after dosing of 80 IU/kg BW IMP

  All PK analyses will be based on the PK set. The following PK parameters will be analysed:

  - Area under the curve (AUC) and AUC_{norm} (normalised for the administered dose)
  - In vivo half-life (T1/2)
  - Maximum plasma concentration (C_{max})
  - Time to reach maximum plasma concentration (T_{max})
  - Mean residence time (MRT)
  - Volume of distribution (Vd)
  - Clearance (CL)
  - Incremental in vivo recovery (IVR)

Pharmacokinetic parameters will be computed for VWF:Ac and FVIII:C vs time profiles. The one-stage (OS) assay for FVIII, actual IMP potencies, and actual sampling times will be used in the calculations. Pharmacokinetic parameters will be derived by non-compartmental methods. To account for residual VWF:Ac and FVIII:C levels the listed parameters will be based on pre-dose-adjusted concentration vs. time profiles (see section 6.1).

- Incremental in-vivo recovery (IVR) of *wilate* for VWF:Ac (VWF:RCo) and FVIII:C (OS) over time (at baseline and at 1, 2, 3, 6, 9, and 12 months of treatment)
- Efficacy of *wilate* in the treatment of spontaneous and traumatic breakthrough BEs based on the proportion of spontaneous and traumatic BEs successfully treated with IMP as assessed by the use of a 4-point ordinal haemostatic efficacy scale (excellent – good – moderate – none).

  To assess the haemostatic efficacy of *wilate* in the treatment of breakthrough BEs during prophylaxis, a frequency distribution of all treated BEs that were successfully treated will be presented overall and by severity, along with an exploratory 95% CI for the proportion of successfully treated BEs.
- Efficacy of *wilate* in surgical prophylaxis

  The following surgery-related parameters will be analysed (analysis will only be performed if more than 3 treatment-emergent surgeries were reported. Otherwise, data will be listed only):
  - Location, severity (minor or major, for definitions see protocol), and type (planned or emergency) of surgery
  - Expected and actual duration of surgical procedure
  - Expected average/maximum and actual blood loss
  - Pre-, intra-, and/or postoperative IMP administration data (only listed)
  - Pre-, intra-, and postoperative VWF:Ac and FVIII plasma levels (only listed)
  - Routine safety laboratory
  - Presence of wound haematomas
  - Vital signs (blood pressure, heart rate, body temperature, and respiratory rate)
  - Details on concomitantly administered medications (except standard anaesthetics)
  - Blood transfusion requirements
  - Brief narrative describing the outcome of the intervention
  - Overall efficacy assessment at the end of the postoperative period by the responsible treating investigator. Predefined assessment criteria will be used
  - Concomitantly administered products (only listed)

- Narrative describing the outcome and efficacy of the intervention (only listed)
- Inhibitor testing (within 3–8 weeks after the end of the surgery, this visit may coincide with another study visit with scheduled inhibitor testing)

Primarily, all obtained data on treatment characteristics (IMP dosages, frequencies, total consumption) and BEs (duration, frequency, efficacy assessment) will be described by providing summary statistics and supporting figures where appropriate.

In general, the efficacy of *wilate* in the treatment of bleeding episodes will also be presented by type (spontaneous, traumatic, postoperative, other), sites (nose, oral cavity, knee, ankle, elbow, arm, leg, intestinal and other. In addition, knee, ankle and elbow sites will be summarized as site 'joint') and severity (minor, moderate, major, life-threatening).

Surgeries and bleeding episodes treated with commercial *wilate* will not be excluded from efficacy analysis of *wilate* in surgical prophylaxis and efficacy analysis of *wilate* in treatment of bleeding episodes, respectively. However, commercial *wilate* will not be included in the dosing analyses.

4.7.3 Exploratory endpoints

Multimer analysis

The exploratory endpoint of this study, which is solely investigated in the hereditary type 3 VWD patients with ≥14.5 kg body weight, is a VWF multimer analysis from the PK samples taken at 15 minutes, and 24 hours after IMP injection, by using multimer analysis using low- and high-resolution electrophoresis gels. In addition, the VWF multimer analysis is performed at baseline in all patients.

The multimeric pattern for each sample will be assessed at an independent laboratory. Gels were run at concentrations of 1.2% (low resolution gel) and 1.6% (medium resolution gel), a normal plasma pool sample served as control

Data from the densitometry readings of the gel will be presented as percentage of the multimer bands relative to the total bands. In the 1.2% gels three groups (bins) of multimer peaks will be analyzed, small multimers (bands 1-5), intermediate multimers (bands 6-10) and large multimers (bands > 10) and a narrative description will be provided in addition. For the 1.6% gels, only the triplets narrative description will be provided in line with the reports of the central laboratory. The frequency distribution of standardized narrative descriptions will be displayed for both, the 1.2% and 1.6% gels.

For the screening samples, descriptive statistics of the three multimer groups/bins will be presented per VWD type and sex and for the corresponding plasma pool values.

In VWD type 3 patients, descriptive statistics of the multimer groups will be analysed in addition by time point ((i.e. 15 minutes and 24 hours post infusion) including analysis of changes with time (24 hours vs. 15 minutes) as well as in comparison with a normal plasma pool and frequency distribution of standardized narrative description. All individual multimer data will be additionally listed.

Annualized bleeding rates for treated bleedings

All of the analysis described for the primary end point including robustness analysis (see section 4.7.1) will be repeated for treated bleeds only.

Prior annualized total bleeding rates (pTABR)

The historical total number of bleeding episodes under On-Demand treatment/6 month and under prophylactic treatment/≤ 6 month collected at screening will be used to extrapolate the prior TABR ($pTABR_{OD}$ and $pTABR_{PROPH}$) if a sufficient amount of data are available. This analysis will be purely descriptive.

4.8 Safety

All safety analyses will be based on the SAF population.

The analysis of safety will be based on the occurrence of AEs, e.g. results of immunogenicity screening, thrombogenicity monitoring for sustained excessive FVIII plasma levels (and an increased risk of thrombotic events), and safety laboratory testing. Analysis of AEs will focus on treatment emergent adverse events (TEAEs).

4.8.1 Adverse events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) in the version current at the clinical start of the study. The analysis will focus on the incidences and total numbers of treatment-emergent adverse events (TEAEs), i.e., AEs that started or worsened after the first IMP injection. All TEAEs, related TEAEs (i.e., TEAEs at least possibly related to the IMP), and serious TEAEs will be summarised and tabulated according to MedDRA primary system organ class and preferred term.

Other safety parameters (e.g., changes in physical examination findings, Haemophilia Joint Health Score) will be analysed by summary tables or listings.

It is assumed that for each change in intensity, relationship or seriousness of an AE a new entry of the AE was recorded in the data capture database; hence such cases will be analysed like different phases of the same AE.

Incidence tables, i.e. frequency tables of subjects experiencing at least one occasion of the event while at risk (along with the number of different occurrences of the TEAE), will be presented for the following types of adverse events:

- All TEAE irrespective of the causality assessment
- Related TEAEs (‘Probably’ or ‘Possible’)
- TEAEs by worst severity
- Serious TEAEs
- Severe TEAES
- Thromboembolic events

Multiple counts within a PT or SOC (repeated or different included terms or changes in descriptors) will be counted only once for the calculation of incidences.

A listing of "special cases" containing subject identification, age, sex, AE descriptors, start and end of treatment will be prepared for the following types of TEAEs:

- Serious adverse events (SAE)
- Severe TEAES
- Related TEAEs ('Probably' or 'Possible')
- Adverse events which led to death
- Adverse events which led to discontinuation
- Thromboembolic events (TEEs)

Serious non-treatment emergent AEs will be listed separately.

Narratives will not be included in section 14.3.3 but will be provided by medical writing in section 12.3.2 of the CSR. All adverse events (i.e. TEAEs as well as non-treatment emergent events) will be listed in section 16.2 of the CSR. However, only TEAEs will be summarized in the tables.

4.8.2 Vital signs

Vital signs parameters (blood pressure, heart rate, body temperature, and respiratory rate) will be assessed at screening, PK visit, after 1, 2, 3, 6, 9 and 12 months at study completion visits and if applicable during surgery.

Descriptive analyses will be performed for values at visits and changes from baseline.

4.8.3 Laboratory variables

The analysis of the safety parameters (lab values for Haematology) recorded during visits and at surgery will be purely descriptive and presented as summary tables or listings.

Time profiles of the safety laboratory parameters will be analysed by presenting sampling statistics for the values as well as their difference to baseline at each time point. Additionally, frequency tables for values outside the normal ranges will be presented.

Time profiles of the safety laboratory parameters will be analysed by presenting sampling statistics for the values as well as frequency tables for positive findings.

Similarly, time profiles of VWF and FVIII inhibitor testing results will be analysed by presenting sampling statistics for the values as well as frequency tables for number of positive findings, along with 95% Pearson-Clopper CIs.

The thromboembolic risk will be monitored by determination of VWF:Ac during the study and especially postoperatively. Descriptive statistics including changes to pre-infusion will be presented by visit and timepoint (with 95% CI) for visits or by operative day and timepoint for surgeries, respectively.

A by subject list of all abnormal lab values will be displayed. In analyses only scheduled, common time points will be displayed. Results from unscheduled visits will only be used in listings. In such listings the normal ranges as well as an indicator of H/L and CLS will be given.

4.8.4 Global assessments

Not applicable

4.9 Other variables

Results of multimeric patterns for subjects with type 3 VWD ≥ 14.5 kg BW will be listed by subject ID.

4.10 Interim analyses

Not applicable.

5 QUALITY CONTROL

The SAP was reviewed by the TS before signature. Particularly the TS has checked the consistency of the described methods and outputs with the actual version of the study protocol. In addition, a sponsor representative has reviewed the SAP before final approval.

Log files of all SAS® programs used in the analysis will be checked for errors, warnings and suspicious notes by the statistical programmer. All findings will be either eliminated or commented upon. The final version of each program will be stored along with its log file in the electronic archive.

All programs will be validated by the program author or an independent statistical programmer depending on the requested validation level selected in the List of TLFs form (FRM/BS/001.02) for a particular program.

The agreement of the program outputs with the SAP, their consistency and plausibility will be checked by the TS. Moreover, the TS will review the outputs regarding completeness, readability and comprehensibility.

The described process is associated with the 'normal' level of program validation. Additional levels of quality control can be specified in the List of TLFs (see Appendix, 1) for individual outputs.

6 DERIVATIONS AND TRANSFORMATIONS

6.1 Formulas for derived variables

To allow correct assessment of the PK-effect of the applied treatment, the measured concentration vs time profiles for VWF:Ac and FVIII:C will be adjusted for the residual levels of these parameters to increments above residual level. This will be achieved by subtracting the respective pre-dose levels from the measured concentrations, i.e. $C_n(adj) = C_n - C_0$. If this operation should result in a negative value, then $C_n(adj)$ will be set to zero.

Variable	Definition / Derivation
BMI	Weight [kg] / (height [m])^2
Durations between two dates	Later date minus earlier date plus 1, expressed in days. (Remark: Duration will be 1, if both dates are the same.)
Time in study	Date of study completion – date of screening +1 (date of initial screening for subject 33-31-01/02)
Surgery Period (days)	Individual surgery period: last date of IMP in context of surgery (reason = "Prophylaxis after surgery" or "Surgery") – date of surgery + 1 or 1 day (i.e. day of surgery) in case surgery not treated/no treatment information available. Surgery period: Sum of individual surgery periods per subject. All BEs at day of surgery with onset after start of surgery and all BEs occurring under post-operative prophylaxis (reason = "Prophylaxis after surgery") will be excluded from the calculation of ABRs
Prior Prophylactic treatment phase (days)	(date of screening – date subject switched to prophylaxis prior to study) + 1
Prior Total Annualized Bleeding Rate Prophylaxis ($pTABR_{PROPH}$)	Number of bleedings under prior prophylactic treatment phase / (prior prophylactic treatment phase /365.25) This will only be included in the analysis if the treatment phase is at least 4 months
Prior Total Annualized Bleeding Rate On-Demand $pTABR_{OD}$)	Number of bleeding episodes under prior On-Demand treatment/6 month * 2
Prophylactic treatment phase (days)	(last date of IMP + 2 OR completion date, whichever occurred earlier) – first date of prophylactic IMP after the PK visit +1) – Surgery period.

Variable	Definition / Derivation
Prophylactic treatment phase (Special case of patient 33-31-01/02)	Initial prophylactic treatment phase + Regular 12-Months prophylactic treatment phase
Initial Prophylactic treatment phase (Special case of patient 33-31-01/02)	((last date of IMP before premature termination + 2 OR premature termination date, whichever occurred earlier) – first date of prophylactic IMP after the initial PK visit +1). Surgery period is not applicable
Regular Prophylactic treatment phase (Special case of patient 33-31-01/02)	((last date of IMP after re-enrolment + 2 OR regular completion date, whichever occurred earlier) – first date of IMP at second Screening/IVR visit +1). Surgery period is not applicable
Total Annualized Bleeding Rate Prophylaxis (TABR)	Number of bleedings under prophylactic treatment phase / (prophylactic treatment phase /365.25)
Spontaneous Annualized Bleeding Rate (SABR)	Number of spontaneous bleedings under prophylactic treatment phase / (prophylactic treatment phase/365.25)
Traumatic Annualized Bleeding Rate (TRABR)	Number of traumatic bleedings under prophylactic treatment phase / (prophylactic treatment phase/365.25)
Joint/Non-Joint Annualized Bleeding Rate (JABR/NJABR)	Number of joint/non-joint bleedings under prophylactic treatment phase / (prophylactic treatment phase/365.25)
Actual potency	Potency of IMP (IU) for FVIII (OS) determined by central laboratory measurements, potency for VWF:Ac (VWF:RCo) obtained from the Certificates of Analysis. The analysis of PK and IVR assessment will be based on actual potencies
Labelled potency	Potency of IMP (IU) based on label of vial (IU). Dosing analyses will be based on labelled potency
AUC	Area under the curve from baseline to infinity $AUC = \sum\left(\frac{(C_n + C_{n+1})}{2} \cdot \Delta t\right) + \frac{C_{last}}{K}$ (C_{last} is the last available measurement)
AUC_{norm}	AUC normalized for the administered dose
AUMC	Area under the moment curve (from baseline to infinity) $AUMC = \sum\left(\frac{(t_n \cdot C_n + t_{n+1}C_{n+1})}{2} \cdot \Delta t\right) + \frac{C_{last}}{K^2} + \frac{t_{last} \cdot C_{last}}{K}$
CL	Clearance

Variable	Definition / Derivation
	$CL = \frac{D}{AUC}$ where D is the actual dose administered .
C_0	FVIII/VWF activity before IPM administration
C_{max}	Maximum -FVIII/VWF activity in plasma. Maximal measured activity after end of IMP infusion (peak activity)
ED	Exposure day = each calendar day the subject received at least one dose of IMP
Geometric mean	The exponential of the Mean log-concentrations $exp\left[\frac{1}{n}\sum_{i=1}^{n} lnX_i\right]$
Incremental In Vivo recovery (IVR)	$IVR = \frac{(C_{max} - C_0) \cdot BW}{D}$ where BW stands for the body weight in kg and D is the dose according to the actual potency of the VWF/FVIII concentrate as described in above
MRT	Mean residence time $MRT = \frac{AUMC}{AUC}$
$T_{1/2}$	In vivo half-life using linear regression on the terminal phase of the natural logarithm of the concentration; $T_{½} = \frac{\ln(2)}{K}$ (where K, the elimination rate constant, is determined as the slope of the regression line)
Vd	Volume of distribution at steady state: Vd=CL·MRT
Incremental in vivo recovery (IVR)	$IVR = \frac{(C_{max} - C_0) \cdot BW}{D}$ where BW = body weight in kg and D = dose of IMP
Haemostatic success (in treatment of bleeding episodes and surgeries)	Success: efficacy rating ‘excellent’ or ‘good’ Non-Success: efficacy rating ‘moderate’ or ‘none’ or ‘missing’

6.2 Transformations to be applied

For the calculation of PK parameters (AUC, half-life) and statistics (geometric means and standard deviations) plasma concentration values will be log-transformed (natural logarithms).

7 REFERENCES

No specific references were used.

8 STANDARDS USED IN PREPARATION OF STATISTICAL OUTPUTS

The below conventions will be followed as agreed with the Sponsor.

8.1 Programming

- One SAS program should create only one output.
- One output file can contain different output types (e.g. descriptive and inferential).
- Individual output files will be created in MS Word format (Rich Text Format, RTF).
- Once delivered to the sponsor, numbering of TLFs will not be altered, unless agreed

8.2 Layout

- TLFs will be produced in landscape format
- TLFs will have a minimum 2 cm on every side
- TLFs will be produced using the Courier New font, size 8
- Section numbering of TLFs will follow ICH E3 guideline.
- Numbering of TLFs will follow the convention XXX-YY, where XXX stands for a (sub-)section number of the ICH E3 guideline and YY represents the sequence number of the output within the section (e.g. 14.3.1-4, 16.2.7-2). A dash ('-') will always be used to separate section numbers from output sequence numbers.
- Titles and footnotes for figures will also be in Courier New font, size 8.
- Tables and listings will be in black and white (no colour), figures may include only colour that can be distinguished when printed on a grey-scale printer
- Text styles, such as bolding, italics, borders, shading, and superscripted and sub-scripted text, will be used sparingly in the TLFs
- The ANSI character set will be used in the TLFs. Certain subscripts and super-scripts (e.g., m^2, AUC_{norm}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, unless they are derived directly from the data

8.3 Headers, Titles and Footnotes

- All output will have the following header at the top left of each page showing the study ID, the date of output generation and an internal pagination, where Y stands for the total number of pages in the pertaining output.

- Also, all TLFs will have the following footer, identifying the generating SAS program (XXX.SAS), a reference to the relevant subject listing and the date of the data snapshot:

SAS program: <XXX>.sas Ref. list X.X.X-YY Data status: YYYY-MM-DD

- Each TLF will bear a title which is repeated on each page of the output.
- The title at the top of the page will be horizontally cantered in bold font.
- A blank line will separate the title from the body of the output.
- The title will consist of an Output number, a descriptive title and a description of the presented analysis set (if applicable).
- The title will have the following general appearance:

Table / Figure / List XX.X.X-YY
Descriptive Title line 1
Descriptive Title line 2
(All subjects in the FAS, N=nnn)

- Each new footnote should start on a new line, where possible.
- Preferably, footnotes should be left justified. When extending beyond a single line, a manual linefeed should be inserted to avoid meaning distortion.
- An automatic footnote '(continued)' will appear at the bottom of TLFs that extend over more than one page.

8.4 General Conventions

- For measured variables column headers should include the unit in their description
- The order of treatment arms in the TLFs will be consistent throughout the entire TLF presentation
- Alphanumeric values are preferably displayed left-justified
- Dates are presented left-justified
- Integer numbers (e.g., counts) can be cantered or right-aligned
- Numbers containing fractional portions will be decimal-aligned.
- Fractional numbers with absolute value less than 1 will carry a leading zero, i.e. 0.123 not .123.
- Units of measured or derived variables will be included where appropriate
- Unless otherwise warranted, the estimated mean, median and quartiles for a set of values will be displayed with 1 more significant digit than the original values, and standard deviations with 2 more significant digits. The minimum and maximum should report the same significant digits as the original values.

- P-values are output in the format: "0.xxxx", where xxxx is the value rounded to 4 decimal places. P-values less than 0.0001 will be presented as <0.0001.
- Precision of percentages displayed will depend on the total study size. For studies with less than 1000 subjects values will be presented with one decimal place. For studies with more than 1000 subjects, values will be presented with two decimal places.
- Tabular display of data for medical history, prior/concomitant medications and all tabular displays of adverse event data are generally presented by body system, treatment class, or SOC according to the Internationally Agreed Sorting Order of the MedDRA, unless otherwise agreed.
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis (sub-) population presented.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, an explanatory text will be added to clarify that multiple answers were possible.
- Missing values will be displayed either by a double-dash ("--") or as "NA" (='not available/applicable'), whichever is appropriate.
- Dates are displayed in according to ISO date/time format as YYYY-MM-DD, e.g. 2010 03 24. Missing dates may be represented as "NA", if not available/applicable.
- Clock times are displayed as HH:MM or HH:MM:SS based on 24-hour clock

APPENDICES

1. List of Tables, Listings, Figures

A complete List of tables, listings, figures (TLFs) will be given in a separate document which can be updated without updating the SAP. The List will serve as a reference for both the Sponsor, the TS and the SP and describes the entire set of statistical output to be produced. Therefore, this List will be versioned and approved by both Ergomed and Sponsor before commencing the statistical programming.

All subject listings will contain in addition to the subject identification the analysis set and the treatment group.