# Statistical Analysis Plan (SAP)

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| Sponsor: | Octapharma |
| Study Title: | Clinical Study to Investigate the Efficacy and Safety of Wilate during Prophylaxis in Previously Treated Patients with VWD |
| Protocol Version/Date: | Ver. 07, 2021-03-01; Ver. 08, 2021-03-01 (Ukraine only) |
| SAP Version/Date: | Ver. 6.0, 2022-09-23 |
| Supersedes SAP Version: | Ver. 5.0, 2022-05-18 |
| 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<br>Affiliation, Function | Signature: | Date: |
|---|---|---|
| [redacted]<br>Ergomed, Trial Statistician | | |

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<br>Affiliation, Function | Signature: | Date: |
|---|---|---|
| [redacted]<br>Octapharma | | |
| [redacted]<br>Octapharma | | |

**Revision history**

| SAP Version | Version date | Reason(s) for change |
|---|---|---|
| 1.0 | 2018-12-18 | Initial version |
| 1.1 | 2019-02-08 | Trial Flow Charts were adapted. |
| 2.0 | 2019-06-21 | - adding age and race subgroup analyses<br>- adding non-parametric test for primary endpoint TABR<br>- adapting to new IVR visit schedule<br>- addressing handling of menstrual bleeds<br>- adding comparisons with historical data obtained during on-demand treatment periods |
| 3.0 | 2020-03-26 | - changing to new SAP template,<br>- addressing changes in protocol versions 05 and 06 respectively protocol amendment #3 and #1-UKA |
| 4.0 | 2022-05-10 | - Modifications and addition of definitions/formulas for derived variables in section 6.1.<br>- Definition for modified FAS and PK PP set added.<br>- For comparison of annualized bleeding rates, instead of a paired t-test for the log-transformed data a negative binomial counting regression model (GLIM) will be used (section 2.2)<br>- Usage of on-demand run-in trial data defined in detail and adapted to the fact that all subjects participated in previous WIL-29 study (usage of retrospective measurements is not applicable)<br>- Further changes after cross-check with protocol and as requested by sponsor as well as minor changes in wording |
| 5.0 | 2022-05-18 | - Protocol Version/Date on page 1 set to current versions 07 (2021-03-01) and 08 Ukraine only (2021-03-01) |
| 6.0 | 2022-09-23 | - The primary analysis set for efficacy was changed from FAS to mFAS to exclude subjects for whom laboratory results did not confirm patient's eligibility regarding inclusion criterion 2 from primary efficacy analysis<br>- Calculation of changes to baseline is not needed for Incremental IVR of Wilate over time<br>- Calculation of PK parameters is based on concentrations adjusted for residual pre-dose levels<br>- Deletion of analysis: frequency distribution of severity for breakthrough bleedings with 95% CIs |

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# LIST OF ABBREVIATIONS

| Abbreviation | Description |
|---|---|
| $ABR_{od}$ | Annualized bleeding rate under on-demand treatment (WIL-29 run-in study) |
| ABRpr | Annualized bleeding rate under prophylactic treatment (study WIL-31) |
| ADR | Adverse drug reaction |
| AE | Adverse Event |
| ALAT | ALanine Amino Transferase |
| ASAT | ASpartate Transaminase |
| BE | Bleeding Episode |
| BMI | Body Mass Index |
| BW | Body Weight |
| CHR | Chromogenic assay |
| CI | Confidence Interval |
| CL | Clearance |
| $C_0$ | Last concentration before IMP administration |
| $C_{max}$ | Maximum Plasma Concentration |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CSR | Clinical Study Report |
| DMP | Data Management Plan |
| DRM | Database Review Meeting |
| DVP | Data Validation Plan |
| ED | Exposure Day |
| eCRF | Electronic Case Report Form |
| FAS | Full Analysis Set |
| FVIII | Coagulation Factor VIII |
| FVIII:C | Factor VIII-coagulant |
| HJHS | Hemophilia Joint Health Score |
| HMABR | Heavy Menstrual Annualized Bleeding Rate |
| ID | Identifier |
| IMP | Investigational Medicinal Product |
| ITT | Intention-To-Treat |
| IU | International Unit |
| IV | Intravenous |
| IVR | Incremental in Vivo Recovery |
| LOCF | Last Observation Carried Forward |
| mFAS | modified Full Analysis Set |
| PK-PP | Pharmacokinetic Per-Protocol set |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRT | Mean Residence Time |
| N | Number of Subjects/Observations |
| OS | One-stage assay |
| POP | Postoperative |
| PBAC | Pictorial Blood Assessment Chart |
| PK | Pharmacokinetic, Pharmacokinetic set |
| PP | Per-Protocol |
| PT | Preferred Term |

| Abbreviation | Description |
|---|---|
| PROMIS-29 | Patient-Reported Outcomes Measurement Information System |
| PT | Preferred Term |
| QC | Quality Control |
| RBC | Red Blood Cell count |
| SAE | Serious Adverse Event |
| SAF | Safety Analysis Set |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis Software package |
| SD | Standard Deviation |
| SP | Statistical Programmer |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SABR | Spontaneous Annualized Bleeding Rate |
| SURG | Surgery analysis set |
| TABR | Total Annualized Bleeding Rate |
| TRABR | Traumatic Annualized Bleeding Rate |
| TEAE | Treatment Emergent Adverse Event |
| TLFs | Tables, Listings, Figures |
| TS | Trial Statistician |
| VWD | Von Willebrand Disease |
| VWF | Von Willebrand Factor |
| VWF:Ac | VWF activity |
| VWF:GP1bM | Assay based on the spontaneous binding of VWF to a gain-of-function mutant GP1b fragment |
| VWF:RCo | Ristocetin cofactor activity; assay that uses platelets and ristocetin |
| WBC | White Blood Cell count |
| WHO | World Health Organization |

# 1 STUDY INFORMATION

## 1.1 Primary objective

The primary objective of this study is to determine the efficacy of *Wilate* in the prophylactic treatment of previously treated patients with type 3, type 2 except N, and severe type 1 VWD.

## 1.2 Secondary objective

The secondary objectives of this study are:

- Assess the incremental IVR of VWF:Ac and FVIII:C over time (at baseline, and at 1, 2, 3, 6, 9 and 12 months of treatment)
- Determine the pharmacokinetics (PK) of *Wilate* for VWF:Ac and FVIII:C in paediatric patients aged 6–16 years
- Assess the safety and tolerability of *Wilate* during prophylaxis
- Determine *Wilate* consumption data

## 1.3 Additional objective

Additional objectives of this study are to:

- Determine the efficacy of *Wilate* in the treatment of breakthrough bleeding episodes (BEs)
- Determine the efficacy of *Wilate* in surgical prophylaxis
- Assess patients' Quality of Life (QoL) during prophylaxis with *Wilate*
- Assess patients' joint status using the Hemophilia Joint Health Score (HJHS)
- Assess the menstrual bleeding intensity of female patients of child-bearing potential (based on PBAC score)

## 1.4 Study design

This study is designed as a prospective, non-controlled, international, multi-center phase 3 study.

It is intended to compare the prospectively obtained assessments under a prophylactic treatment regimen with similar assessment under an on-demand treatment regimen. To achieve this, retrospective data from the patient's medical records or patient data obtained in a similar (prospective) study with an on-demand treatment regimen will be used for the analysis.

Further details are given in the overview on next page.

## 1.5 Planned sample size

Overall, 28 patients will be enrolled in this study, including at least 5 patients with VWD type 3, at least 5 patients aged 6–11 years, and at least 5 patients aged 12–16.

Assuming a mean total annualized bleeding rate (TABR) ratio ($TABR_{pr}$ / $TABR_{od}$) of 0.25 with a correlation of 0.5 between the two treatment regimes, a coefficient of variation of 10 in on-demand treatment, and a coefficient of variation of 10 in prophylactic treatment, 25 patients will be needed to reject the null hypothesis

$$H_0: \text{mean}(TABR_{pr} / TABR_{od}) \geq 0.5$$

in favor of

$$H_1: \text{mean}(TABR_{pr} / TABR_{od}) < 0.5$$

with a type one error of 0.025 and power of 80% using a paired t-test for log-transformed data.

$TABR_{pr}$ is defined as the total annual bleeding rate in the prophylactic treatment and $TABR_{od}$ is defined as the total annual bleeding rate in the matching on-demand treatment period.



# 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 the Data Capture System OPVerdi via validated SAS programs. If applicable external data will also be transferred to SAS for presentation of these data in the statistical analyses.

The SAP will be finalized before database review meeting after agreement with the Sponsor.

## 2.2 Deviations from the trial protocol with regard to statistical analyses

Due to the reporting of non-confirmed eligibility, the primary and secondary efficacy analyses will also be performed for the mFAS (see section 3.3).
Contrary to initial assumptions, patients may have documented 0 bleeding episodes during the prophylactic treatment phase. This would contradict the assumption of a log-normally distributed TABR and make the calculation of logarithms of the TABRs impossible. Hence, instead of the originally planned paired t-test for the log-transformed data, now the use of a negative binomial counting regression model (GLIM) with treatment regimen as main effect and treatment period as offset parameter is implemented for the analysis of the primary efficacy parameter.
Such counting regression models will also be used for the analysis of similarly defined secondary and exploratory endpoints (e.g. SABR).

## 2.3 Individual protocol deviations

Any deviation from protocol will be discussed case by case before database lock whether the deviation has to be regarded as minor or as major, and whether an observed deviation will lead to exclusion from particular analysis populations.

Examples for minor protocol violations may be deviations from scheduled investigation time.

Criteria for important protocol violations will at least include:

- Any substantial violation of in- or exclusion criteria.
- Use of concomitant medication that may interfere with the assessment of efficacy.

- Substantial deviations in frequency, duration and/or dosing of the prophylactic treatment regimen.

The final decision about the classification of individual protocol deviations and their consequences regarding assignment of subjects to analysis sets will be made during the data review meeting (DRM). A complete listing of protocol deviations and the judgment for assessment of subject disposition will be approved by the Sponsor and signed before database lock. All deviations as well as the disposition of each subject will be recorded in separate database members that will become part of the study database. A description of all important protocol violations will be included in the table part of the CSR.



# 3 ANALYSIS POPULATIONS

The disposition of patients will be displayed according to the following analysis populations:

- Safety (SAF) set
- Full Analysis set (FAS)
- Modified Full Analysis set (mFAS)
- Per-Protocol (PP) set
- Surgery (SURG) set
- Pharmacokinetic (PK) set
- Pharmacokinetic Per-Protocol (PK PP) set

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.

## 3.1 Safety Set

The **safety (SAF) set** will include all subjects who received at least one dose of IMP.

## 3.2 Full Analysis Set

The **full analysis set (FAS)** defined according to the intention-to-treat (ITT) principle will include all enrolled subjects who received at least one dose of IMP after the Baseline IVR Visit in adults or the Baseline PK Visit in children.

## 3.3 Modified Full Analysis Set

The **modified full analysis set (mFAS)** will be a subset of the FAS excluding all subjects for whom laboratory results did not confirm patient's eligibility, i.e. severe VWD type 1, 2A, 2B, 2M or 3 not confirmed.

### 3.4 Per Protocol Set

The **per-protocol (PP) set**, i.e. a subset of the FAS, will exclude subjects with major protocol deviations which may have an impact on the evaluation of the primary study outcome parameter (major protocol deviations as defined during DRM).

### 3.5 Surgery Set

The **surgery (SURG) set** will be a subset of the FAS, containing all subjects who underwent a surgical procedure treated with IMP prior to start of surgery during their Prophylactic Treatment Phase.

### 3.6 Pharmacokinetic Set

The **pharmacokinetic (PK) set** will be a subset of the FAS containing all subjects with a pharmacokinetic assessment.

### 3.7 Pharmacokinetic Per-Protocol Set

The **pharmacokinetic Per-Protocol (PK PP) set** will be a subset of the PK, excluding all subjects for whom laboratory results did not confirm patient's eligibility, i.e. severe VWD type 1, 2A, 2B, 2M or 3 not confirmed and excluding patients with an inhibitor to von Willebrand factor or factor FVIII at PK visit. Invalid samples/PK profiles (e.g. hemolyzed samples) will be excluded from PK-analysis as defined during DRM.

### 3.8 Subgroup analyses

The analyses of the efficacy endpoints ‘efficacy of prophylactic treatment’ and ‘efficacy in treatment of breakthrough BEs’ will be presented in the following subgroups:

- Age groups (‘6 to 11, 12 to 16 and >16 years’).
- VWD type (‘severe type 1’, ‘type 2’ and ‘type 3’)
- Sex (‘Female’, ‘Male’)
- Race, according to CDISC Controlled Terminology (dependent on the number of subjects per race)

The safety analysis will be presented by the following subgroup:

- Age groups (‘6 to 11, 12 to 16 and >16 years’).

# 4 STATISTICAL ANALYSES

All statistical analyses will be performed using the SAS® software (Version 9.4 or later). Pharmacokinetic parameters will be calculated using the WinNonlin software for Windows, version 7.0 or later using a non-compartment model (for definitions see section 8.1 of this SAP):

Descriptive statistics will always be given for the entire population.

The analysis of safety will be based on the SAF set.

Analysis of the primary endpoint will be performed on the FAS, mFAS and PP set, where the primary analysis set will be the mFAS.

For secondary and other endpoints (except endpoints regarding surgeries), FAS, mFAS and PP analyses will be carried out, unless the latter analysis sets differ by no more than 5% of patients in the mFAS.

Analysis of the efficacy and safety of *Wilate* in surgeries will be based on the SURG set.

If not stated otherwise the following standard descriptive statistics will be presented:

Descriptive statistics for continuous data

Number of subjects (N), arithmetic mean, standard deviation (SD), minimum, lower quartile, median, upper quartile and maximum will be presented. These descriptive statistics will be determined for measured values and for differences to baseline.

Descriptive statistics for categorical data

Absolute frequencies (N) will be presented with 0, relative frequencies (%) with at least 1 decimal. For changes from baseline, shift tables may be generated.

Inferential statistics

If not stated otherwise all statistical tests will be performed as described in the corresponding sections below.

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.

All confidence intervals (CI) will be derived two-sided and at a confidence probability of $1-\alpha = 0.95$.

Listings

All subject data will be listed by subject. Identification variable will be the subject ID (composed of study, center and subject number separated by a hyphen, e.g. '31-01-01'. Any derived data listed will also be stored permanently and will be calculated as outlined in section 6.1 of this SAP.

## 4.1 Conventions

### 4.1.1 Baseline definition

Assessments at screening visit or the first IVR measurement (at PK or IVR visit, respectively) whatever is closest to start of prophylaxis are considered as baseline.

### 4.1.2 Missing data

In case of missing body weight documentation, data will be imputed using the Last Observation Carried Forward (LOCF) approach to calculate the dose per kg body weight (IU/kg).

In case of missing date/time documentations for IVR and PK samplings the corresponding scheduled time point will be used for analysis.

No further imputations for missing data will be performed.

Calculations pertaining to the derivation of annual bleeding rates will be based on documented time periods only.

### 4.1.3 Pooling of centers

All tables will be presented in total over all participating countries and centers. The distribution of number of subjects per country and center will be presented in the disposition section of the report.

### 4.1.4 Use of measurements from on-demand non-interventional run-in study (WIL-29)

Apart from analyzing the efficacy of Wilate in the prophylactic treatment of VWD based on annualized bleeding rates, it is also of interest to compare data with annualized bleeding rated of the same patients under an on-demand treatment schedule. To achieve this, data from those patients that also participated in a previous on-demand run-in study (WIL-29) will be used in the analysis data for the current study. This includes duration of On-demand phase, number of bleeding episodes and annualized bleeding rates for total, spontaneous, traumatic, and heavy menstrual bleeds.

For females with childbearing potential, it is of interest to compare their differences in median PBAC scores under prophylaxis with scores under on-demand treatment. For this purpose, all total PBAC scores collected during study WIL-29 will be stored in the WIL-31 database and the Wilcoxon matched pair sign-rank test will be used for statistical comparison.

The statistical methods for such exploratory comparisons of on-demand to prophylactic treatment schedule will be based on paired, or repeated-measurement data.

## 4.2 Demographic and other background data

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, FAS and mFAS 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:

- ABO blood group
- VWF:Ac and FVIII levels at screening, VWF multimer pattern for VWD type 2A, and genotype for VWD type 2B
- Vital Signs (Systolic and diastolic blood pressure, pulse, respiratory rate, and body temperature) at screening
- Physical examination (normal/abnormal) at screening
- Results of Parvovirus B19 antibodies at baseline IVR visit
- Urine pregnancy test (in female patients of child-bearing potential)
- Historical annual bleeding rates (ABR)
- Hemophilia Joint Health Score (HJHS) at baseline
- Target joint(s) at baseline

Historical PBAC scores (total scores documented under on-demand treatment from run-in study WIL-29)

### 4.3 IMP exposure, compliance

Prophylactic treatment will be administered 2 – 3 times per week at a dose of 20 – 40 IU/kg BW for 12 months.

In case of unacceptably frequent spontaneous breakthrough BEs (i.e., more than 2 spontaneous BEs or 1 major spontaneous BE within a 30-day period), the dose of *Wilate* should be increased by approximately 5 IU/kg (depending on the entire content of the additional vial(s) that need(s) to be reconstituted).

Overall summaries will be provided for

- Number of Injections
- Number of Exposure Days
- Total Dose (IU)
- Dose (IU/kg.)
- Reason for Administration

For the FAS and the mFAS population the following parameters will be summarized by frequency tables of descriptive statistics:

- Number of subjects treated prophylactically among all enrolled subjects
- Treatment regimen, dosage, changes, or interruptions in prophylactic treatments
- Number of injections
- Overall period of exposure (from first- to last dose of IMP)
- Number of exposure days

- Amount (IU) of *Wilate* used (per month, per year, exposure day and injection, and in total)
- Normalized dose (IU/kg) of *Wilate* used (per month, per year, exposure day and injection, and in total)
- Frequency and relative magnitude of dose changes: increased and decreased doses of *Wilate* used to treat individual BEs
- Frequency and relative magnitude of dose changes: in the doses per injection and changes in the total dose used to treat subsequent BEs of the same site (e.g. elbow, knee, etc.) in the same patient

All IMP treatment details will be listed for the FAS population.

Furthermore, the *Wilate* batches and their actual potencies will be included in the listing of individual doses.

### 4.4 Medical history, physical examination

Data on medical history will only 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.

Concomitant 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.



### 4.6 Concomitant non-pharmacological measures, pre-medication

Not applicable.

### 4.7 Efficacy

The analysis of the efficacy of prophylactic treatment with *Wilate* will be based on the FAS, mFAS and additionally on the PP set if the latter populations differ by >5% of the mFAS.

The efficacy of Wilate in prophylactic treatment will be presented based on the total annualized bleeding rate (TABR) – see section 4.7.1.

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.

### 4.7.1 Primary Endpoint

Primary objective of this study is to demonstrate that the total annualized bleeding rate (TABR) during prophylactic treatment lowers the patients' TABR during on-demand treatment by more than 50%.

TABR will be calculated as the total number of spontaneous, traumatic and other bleeds (excluding menstrual bleeds) in the time period between first prophylactic dose of IMP and the day of the last dose of IMP (+ 2 days wash-out), divided by the duration (in years) between first dose of prophylactic IMP and the day of last dose of IMP (+ 2 days wash-out). Surgery periods, and BEs occurring within these periods, will be excluded from the calculation of TABR. Menstrual bleeds of any severity will not be included in this calculation. In female patients with child-bearing potential heavy menstrual bleeds will be reported and analyzed separately.

For this efficacy assessment the individual annualized bleeding rates under prophylactic treatment in this study will be compared to the annualized bleeding rates recorded for the same patient during a previous, non-interventional study, (WIL-29).

To test whether the mean TABR during prophylactic treatment ($TABR_{pr}$) is less than half the historical mean TABR during on-demand treatment ($TABR_{od}$), the following pair of hypotheses will be tested in the context of negative binomial counting regression model:

(*)$H_0$: $\text{mean}(TABR_{pr} / TABR_{od}) \geq 0.5$ vs $H_1$: $\text{mean}(TABR_{pr} / TABR_{od}) < 0.5$

at a one-sided alpha level of 2.5%. A corresponding two-sided 95% CI for the different TABRs and their ratio will also be provided.

### 4.7.2 Secondary Endpoints

Secondary endpoints are:

- Spontaneous annualized bleeding rate (SABR), calculated in analogy with TABR
- Incremental IVR of Wilate for VWF:Ac (VWF:Rco and VWF:GP1bM) and FVIII:C (OS and CHR) over time (at baseline and at 1, 2, 3, 6, 9, and 12 months of treatment)
- For paediatric patients, baseline PK profile characteristics of VWF:Ac (VWF:Rco) and FVIII:C (OS and CHR) based on blood samples taken pre-dose and 1, 3, 9, 24, 48, and 72 hours after dosing
- Wilate consumption data (VWF/FVIII IU/kg per month per patient) for prophylaxis

The statistical analysis of the secondary endpoints will be descriptive, including exploratory 95% confidence intervals.

For the secondary endpoint SABR descriptive statistics will be tabulated. Comparisons with on-demand treatment similar to TABR analysis will be performed.

Regarding the IMP administration data, the following parameters will be listed:

- Dates and times of IMP injections
- Doses of IMP in IU and IU/kg and IMP batch numbers
- Reason for IMP injection (prophylaxis, treatment of BE, surgery)

Descriptive statistics will be determined for time in study, exposure days, number of infusions and dosages of IMP overall and by reason for IMP injection.

Descriptive statistics including changes to pre-infusion will be tabulated for VWF:Ac (VWF:Rco and VWF:GP1bM) at baseline IVR visit, at 1, 2, 3, 6, 9 months IVR visit and at study completion visit.

### 4.7.3 Exploratory Endpoints

Exploratory endpoints are:

- Efficacy of Wilate in the treatment of breakthrough BEs based on the proportion of BEs successfully treated with Wilate
- Efficacy of Wilate in surgical prophylaxis based on the proportion of surgeries successfully treated with Wilate
- QoL based on the scores of PROMIS-29 for all patients, SF-36v2 for patients aged ≥16 years, and SF-10 for patients aged 6–15 years
- Hemophilia Joint Health Score (HJHS)
- Pictorial Blood Loss Assessment Chart (PBAC) score for menstrual bleeds
- Traumatic annualized bleeding rate (TRABR), calculated in analogy with TABR
- Heavy Menstrual Annualized Bleeding Rate (HMABR) for females with childbearing potential, calculated in analogy with TABR

*Annualized bleeding rates*

Comparisons with bleeding rates (TRABR, HMABR) under on-demand treatment will follow the same approach as for TABR.

*Sensitivity analyses*

ABR endpoints may be influenced by patient's medical conditions that by themselves are associated with an increased rate of spontaneous bleedings. Hence the robustness of the primary results will be investigated by additionally presenting the ABR analysis (descriptive as well as inferential) when subjects with such identified bleedings are excluded.

To study the sensitivity of results with respect to bleedings that are scheduled to occur very frequently but are mainly caused by an underlying medical condition other than VWD (gastrointestinal bleeds related to Ulcer and spontaneous oral cavity bleeds related to Gingivitis) a separate analysis for TABR and SABR will be performed comparing the ABRs under on-demand and prophylaxis excluding subjects suffering from those types of bleeding episodes.

*Efficacy in the Treatment of Breakthrough BEs*

For any BE occurring during study, the following data will be recorded:

- BE type (spontaneous, traumatic, postoperative, other)
- BE site
- BE severity (minor, major)
- Date and time the BE first occurred or was first noticed

- Date and time the BE ended
- IMP administration data

Descriptive statistics will be provided for the number of bleedings overall and by site. Absolute and relative frequencies for the bleeding site, the bleeding type and the bleeding severity will be tabulated.

At the end of each BE treated with Wilate, treatment efficacy will be assessed by the patient (together with the investigator in case of on-site treatment). The efficacy assessment of treatment of BEs includes the categories 'excellent', 'good', 'moderate' and 'none'. All efficacy ratings assessed as either 'excellent' or 'good' will be considered 'successfully treated.'

*Efficacy in the surgical prophylaxis*

Efficacy in surgical prophylaxis will be analyzed descriptively, presenting summary tables and listing on all aspects of surgical treatment and procedures as well as efficacy ratings.

The following surgery-related parameters will be presented:

- 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 FVIII:C and VWF:Ac plasma levels (dependent on the availability of data)
- Routine safety laboratory
- Details on concomitantly administered products, except standard anesthetic products (only listed)
- Blood transfusion requirements (only listed)
- Brief narrative describing the outcome of the intervention (only listed)
- Assessment of efficacy of surgical prophylaxis:
  1. at the end of surgery by the surgeon
  2. at end of the postoperative period by the hematologist
  3. overall efficacy assessment taking both the intra- and postoperative assessments into account, assessed by the Investigator.
- Number of successfully treated surgeries ('excellent' or 'good' overall efficacy rating)

Procedures that meet the following criteria are considered as 'major' surgeries. All other procedures are considered 'minor'

- General or spinal anaesthesia required
- Opening into the great body cavities required
- Severe haemorrhage during surgery possible
- Haemostatic therapy for at least 6 days required
- Orthopaedic interventions involving joints (ankle, knee, hip, wrist, elbow, shoulder)
- 3rd molar extraction or extraction of ≥3 teeth
- Surgeries/conditions in which the patient's life is at stake

Time periods relative to surgical procedures are defined as:

- Preoperative is defined as the time period of up to 3 hours before the start of surgery.
- The end of surgery is defined as the time immediately after the last surgical suture.
- Postoperative is the period from the end of surgery to the time the patient returns to his or her regular Wilate treatment regimen.

*QoL questionnaires*

The results for the QoL scales (PROMIS-29, SF-36; SF-10 for patients <16 years of age) and different categories will be scored according to the analysis manual. Summary tables will be provided for baseline, 6-months and 12-months visit including changes to baseline.

*HJHS questionnaires*

The results for the HJH-scores over time will be summarized in descriptive tables for each visit including changes to baseline.

*PBAC score (only female patients)*

For female patients, the results of the PBAC score over time will be summarized in descriptive tables for each complete menstrual cycle. Additionally, the differences in intra-individual median PBAC scores under prophylaxis will be compared with scores under on-demand treatment (see also section 4.1.4).

*Annualized rate of heavy (i.e. major) menstrual bleeds*

For the exploratory endpoint Annualized rate of heavy menstrual bleeds descriptive statistics will be tabulated. The annualized rate of heavy menstrual bleeds will be calculated in analogy with TABR.

If possible, the annualized rates of heavy menstrual bleeds under prophylactic treatment in this study will be compared to the annualized rates of heavy menstrual bleeds recorded for the same patient during the previous, non-interventional run-in study.



## 4.8 Pharmacokinetics / Pharmacodynamics

For IVR assessments VWF:Ac (VWF:Rco and VWF:GP1bM) and FVIII:C (measured by both, the chromogenic (CHR) and one-stage assay (OS)) will be analyzed based on actual IMP potency.

Incremental IVR of *Wilate* over time (at baseline, 1, 2, 3, 6, 9 and at 12 months of treatment) will be analyzed in summary tables for each time point . For IVR analysis at baseline the IVRs derived from the paediatric PK profiles will also be included.

For children aged 6 to < 16 concentration versus time profiles will be obtained for VWF:Ac (VWF:Rco and VWF:GP1bM) and FVIII:C (OS and CHR) assays.

Calculation of PK parameters will be based on actual IMP potencies, on concentrations adjusted for residual pre-dose levels and actual time after end of infusion.

The following PK parameters will be derived from the adjusted concentration profiles.

:

- Area under the curve (AUC) and AUC normalized for the administered dose ($AUC_{norm}$)
- In vivo half-life ($T_{½}$)
- 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)

The PK profiles and the PK parameters derived from them will be summarized by descriptive statistics (including geometric means and standard deviations, except for $T_{max}$) as well as the presentation of concentration vs. time plots. All derived PK parameters will be presented in by-patient displays.

PK profiles will additionally be presented graphically on original as well as semi-logarithmic scales as concentration-time curves, individually in spaghetti plots, and overall, showing the sample characteristic by time-point.

As PK data are only collected for children, the mentioned PK results will be presented in total and separately by age groups (‘6 to <11’ and ’12 to <16’ years) as well as by VWD type.

## 4.9 Safety

All safety analyses will be based on the SAF population.

The safety and tolerability of Wilate will be assessed by monitoring adverse events (AEs) throughout the study. The analysis of safety will include the occurrence of AEs, the results of the safety laboratory tests, immunogenicity measurements and the occurrence of parvovirus B19 seroconversions.

### 4.9.1 Adverse events

Adverse events (AEs) will be coded by the Data Management of the CRO according to the Medical Dictionary for Regulatory Activities (MedDRA). Coding will be agreed upon with the Sponsor before database lock (cf. DMP).

All adverse events occurring during study will be listed in appendix 16.2 of the report.

The analysis will include only treatment-emergent adverse events (TEAEs), i.e. all documented AEs that started or worsened after the start of the first IMP infusion. It is assumed that for each increase in intensity of an AE a new entry of the AE will be done by the investigator; hence such cases will be analyzed like different phases of the same AE.

A descriptive analysis will be performed. Incidences will be presented by SOC and incidences of PT within primary SOC sorted according to the Internationally Agreed Order.

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.

Global incidences will be calculated for:

- All TEAE irrespective of the causality assessment
- Related TEAEs ('Probably' or 'Possible'), i.e. Adverse Drug reactions (ADRs)
- TEAEs by worst severity
- Serious TEAEs

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)
- Adverse events which led to death
- Adverse events which led to discontinuation

Serious non-treatment emergent AEs will be listed separately.

### 4.9.2 Vital Signs

Vital signs parameters (systolic/diastolic blood pressure, pulse, body weight, respiratory rates, body temperature) will be assessed at screening, IVR baseline, after 1, 2, 3, 6 and 9 months IVR visit, and at study completion visit. Body weight will also be documented within 12 hours before start of surgery.

Descriptive analyses of values will be performed and changes from baseline (before IMP administration) will be analyzed for vital signs parameters at visits.

### 4.9.3 Safety Laboratory variables

The analysis of the safety lab values for

Hematology: RBCs, WBCs, haemoglobin, haematocrit, and platelet count

Clinical chemistry: Total bilirubin, ALT, AST, blood urea nitrogen, serum create nine

recorded during visits (screening and study completion visit), urine pregnancy test results recorded during visits (screening, 3, 6 and 12 months) and at surgery will be purely descriptive and presented as summary tables or listings.

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

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

To assess the viral safety of *Wilate* incidences of parvovirus B19 seroconversions between IVR baseline and end of study will be estimated along with 95% Pearson-Clopper CIs.

### 4.9.4 Other safety variables

Other safety parameters (e.g., changes in physical examination findings) will be analyzed by summary tables or listings. All abnormal findings from the physical examination will be listed.

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

### 4.10 Other variables

Not applicable.

### 4.11 Interim analyses

Not applicable.

## 5 QUALITY CONTROL

The SAP was reviewed by the trial statistician (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.

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

| Variable | Description |
|---|---|
| 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.) |
| On-Demand period (days) | (Date of study completion – date of screening + 1) - Surgery period.<br>Applicable for historical data from WIL-29 |
| Surgery Period$_{od}$ (days) | Formula for surgery period under on-demand treatment correspond to formula for surgery period under prophylactic treatment but replacing "IMP" by "VCP (von Willebrand factor containing product)". Applicable for historical data from WIL-29 |
| Prophylactic treatment phase (days) | ( (last date of IMP + 2 OR completion date, whatever occurred earlier) – first date of prophylactic IMP +1) – Surgery period. |
| 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.<br>Surgery period: Sum of individual surgery periods per subject.<br>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 |
| Annualized Bleeding Rates On-Demand (ABR$_{od}$) | Formulas for ABR under on-demand treatment correspond to formulas for ABR under prophylactic treatment but replacing "prophylactic treatment phase" by "on-demand period".<br>Individual annualized bleeding rates under on-demand period will be taken from calculated rates in study WIL-29 for all subjects along with total number of bleedings |
| Total Annualized Bleeding Rate Prophylaxis (TABR$_{pr}$) | Number of bleedings under prophylactic treatment phase (except menstrual bleedings) / (prophylactic treatment phase /365.25) |
| Spontaneous Annualized Bleeding Rate Prophylaxis (SABR$_{pr}$) | Number of spontaneous bleedings under prophylactic treatment phase /(prophylactic treatment phase/365.25) |
| Traumatic Annualized Bleeding Rate Prophylaxis (TRABR $_{pr}$) | Number of traumatic bleedings under prophylactic treatment phase / (prophylactic treatment phase/365.25) |
| Heavy Menstrual Annualized Bleeding Rate Prophylaxis (HMABR $_{pr}$) | Heavy Menstrual Annualized Bleeding Rate: Number of heavy menstrual bleedings under prophylactic treatment phase / (prophylactic treatment phase/365.25) |

| Variable | Description |
|---|---|
| ED | Exposure day = each calendar day the subject received IMP |
| $C_0$ | Last concentration before IMP administration |
| $C_{max}$ | Maximum plasma concentration. Maximal measured concentration after end of IMP infusion (peak concentration) |
| $T_{max}$ | Time to reach $C_{max}$ (Timing starts at end of injection) |
| $T_{1/2}$ | In vivo half-life $T_{1/2} = \frac{ln(2)}{K}$<br>$K$ = elimination rate constant, determined as the slope of the regression line) using linear regression on the terminal phase of the logarithm of the concentration |
| AUC | Area under the curve from baseline to infinity<br>$AUC = \sum \left( \frac{(C_n + C_{n+1})}{2} \cdot \Delta t \right) + \frac{C_{last}}{K}$<br>($C_{last}$ is the last available measurement) |
| $AUC_{norm}$ | AUC normalized for the administered dose |
| AUMC | Area under the moment curve (from baseline to infinity)<br>$AUMC = \sum \left( \frac{(t_n \cdot C_n + t_{n+1} C_{n+1})}{2} \cdot \Delta t \right) + \frac{C_{last}}{K^2} + \frac{t_{last} \cdot C_{last}}{K}$ |
| MRT | Mean residence time $MRT = \frac{AUMC}{AUC}$ |
| CL | Clearance $CL = \frac{D}{AUC}$ where $D$ is the actual dose administered |
| Vd | Volume of distribution at steady state: $Vd = CL \cdot MRT$ |
| Incremental in vivo recovery (IVR) | $IVR = \frac{(C_{max} - C_0) \cdot BW}{D}$<br>where BW = body weight in kg and D = dose of IMP |
| Hemostatic success (in treatment of bleeding episodes and surgeries) | Success: efficacy rating ‘excellent’ or ‘good’<br>Non-Success: efficacy rating ‘moderate’ or ‘none’ or ‘missing’ |
| Duplicate test results | If more than one blood sample for the same time point and test has been taken and two valid results are available/have been captured into the database, the mean of the values will be used in analysis |

### 6.2 Algorithm for the Overall Efficacy Assessment for Surgical Prophylaxis

The evaluation of overall efficacy of the treatment in surgeries based on the intraoperative and postoperative assessment is defined as described below:

| Intraoperative assessment | Postoperative assessment | | | |
|---|---|---|---|---|
| | **Excellent** | **Good** | **Moderate** | **None** |
| **Excellent** | Excellent | Good | Good | Moderate |
| **Good** | Good | Good | Moderate | Moderate |
| **Moderate** | Good | Moderate | Moderate | None |
| **None** | Moderate | Moderate | None | None |

## 7 REFERENCES

No specific references were used.

## 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.

Each output page will have an appropriate heading specifying the study ID and abbreviated study title.

Each output page will show a common date and page numbers in the form 'Page [x / y]' where x denotes the current page within an output and y the total number of pages of that output. The output pages will not contain any other sequential page numbering.

All statistical output will identify the underlying analysis set(s) and indicate the number of subjects/events in this set (N) and the number of subjects/events actually contributing to the particular output (n).

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

TFLs will follow the numbering scheme of the ICH E3 guideline.