Statistical Analysis Plan (SAP)

Sponsor:	Octapharma
Study Title:	Prospective, Multicenter, Non-Interventional Study Evaluating the Bleeding Incidence in Patients with Von Willebrand Disease Undergoing On-Demand Treatment
Protocol Version/Date:	Ver. 05; 2020-08-05; Ver. 06; 2020-08-07 (Croatia only)
SAP Version/Date:	Ver. 3.0; 2021-06-25
Supersedes SAP Version:	Ver. 2.0; 2021-06-02
Appendices (external documents):	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]		

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]		

Revision history

SAP Version	Version date	Reason(s) for change
1.0	2020-09-08	Initial version
2.0	2021-06-02	Definition for surgery period and surgery time points for calculation of ABR clarified. Definition of FAS changed to match ITT-principle. Further minor changes after cross check with protocol
3.0	2021-06-25	Ambiguous age group definition corrected

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LIST OF ABBREVIATIONS

Abbreviation	Description
ABR	Annualized bleeding rate
ADR	Adverse Drug Reaction
AE	Adverse Event
BE	Bleeding Episode
CRO	Contract Research Organization
DDVAP	Desmopressin (1-deamino-8-D-arginine vasopressin)
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
FVIII	Factor VIII
GPP	Good Pharmacoepidemiologic Practices
HCP	Health-Care Provider
ICH	International Conference of Harmonization
IEC/IRB	Independent Ethics Committee/Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Study
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	MedDRA Preferred Term
PTP	Previously Treated Patients
QoL	Quality of Life
SABR	Spontaneous Annualized Bleeding Rate
SADR	Serious Adverse Drug Reaction
SF-10	10-Item Short Form Health Survey
SF-36v2	36-Item Short Form Health Survey, version 2
SmPC	Summary of Product Characteristics
SOC	MedDRA System Organ Class
TABR	Total Annualized Bleeding Rate
VCP	Von Willebrand Containing Product
VWD	Von Willebrand Disease
VWF	Von Willebrand Factor
VWF:Ac	Von Willebrand Factor Activity
VWF:Gp1bM	Assay to Determine VWF:Ac Based on Spontaneous Binding of VWF to a Gain-of-Function Mutant Gp1b Fragment
VWF:GP1bR	Assay to Determine VWF:Ac Based on Ristocetin-Induced Binding of VWF to a Recombinant Wild-Type Gp1b Fragment
VWF:RCo	VWF Ristocetin Cofactor

1 STUDY INFORMATION

1.1 Primary objective

The primary objective of this study is to characterize the bleeding and treatment pattern of patients with type 3, type 2 (except 2N), or severe type 1 VWD undergoing routine on-demand treatment with a VWF-Containing Product (VCP).

1.2 Secondary objective

The secondary objectives of this study are to:

- Assess the quality of life (QoL) of VWD patients undergoing on-demand treatment with a VCP
- Assess the safety of the VCP used for on-demand VWD treatment

The following objectives are also pursued except for Croatian centers:

- Determine the effectiveness of the VCP used in the treatment of bleeding episodes (BEs)
- Determine the effectiveness of the VCP used in surgical prophylaxis
- Assess the patients' joint status using the Hemophilia Joint Health Score (HJHS)
- Assess the menstrual bleeding intensity of female patients of child-bearing potential

1.3 Study design

This is a prospective, multicenter, international, non-controlled non-interventional study (NIS).

1.4 Planned sample size

No formal sample size calculations were performed. The sample size of 55 patients was chosen based on feasibility and to allow data summaries to be produced. However, with a sample size of 55, a two-sided 95% confidence interval for the mean ABR will extend ±0.8 from the observed mean, assuming that the standard deviation is 3 or less and the confidence interval is based on the large sample z statistic.

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.

2.2 Deviations from the trial protocol with regard to statistical analyses

For calculation of annualized bleeding rates (ABR) surgery periods will be substracted from the time period under observation, and bleeding episodes occurred during surgery periods will not be counted as defined in protocol. However, the definition of surgery periods has been clarified. Protocol definition "3 hours before the start of surgery to the time the patient returns to

on-demand treatment" was updated to "day of surgery until last VCP treatment for surgery". Bleeding episodes that occurred on the day of surgery but before start of surgery will be counted towards the ABR.

2.3 Individual protocol deviations

As this is a non-interventional study deviations from procedures set out in the study protocol will not necessarily lead to exclusions from analysis populations.

However, violations of important in- or exclusion criteria (e.g. no confirmed von Willebrand disease) or treatment schedule (e.g. prophylactic instead of on-demand treatment) are considered important as they may affect the reliability of analysis results.

The decision about the classification of individual protocol deviations and their consequences regarding assignment of subjects to analysis sets will be made during a 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 along with the disposition of each subject will be recorded in a separate database member that will become part of the study database.

3 ANALYSIS POPULATIONS

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

- Full Analysis set (FAS)
- Per-Protocol (PP) set
- Surgery (SURG) 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. The protocol deviation list should be finalized before database lock.

3.1 Full Analysis Set

The **full analysis (FAS) set** defined according to the intention-to-treat (ITT) principle will include all enrolled subjects.

3.2 Per Protocol Set

The **per-protocol (PP) set** is a subset of the FAS that will exclude subjects with important protocol deviations which may have an impact on the evaluation of the primary study outcome parameter.

3.3 Surgery Set

The **surgery (SURG) set** will be a subset of the FAS, containing all subjects who underwent a surgical procedure treated with any VCP prior to start of surgery.

3.4 Subgroup analyses

The analyses of the efficacy endpoints 'total annualized bleeding rate (TABR)' and 'spontaneous annualized bleeding rate (SABR)' 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')

4 STATISTICAL ANALYSES

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

Descriptive statistics will always be given for the entire population.

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

Analysis of the primary endpoint will be performed on the FAS and PP set.

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

Analysis of the efficacy and safety of VCP 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 where applicable for differences to baseline.

Descriptive statistics for categorical data

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

Inferential statistics

Confirmatory statistical inferences are not planned. Any statistical inferences (e.g. confidence intervals) will be of exploratory nature.

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. '29-01-01'. Any derived data, e.g. TABR, listed will also be stored permanently and will be calculated as outlined in section of this SAP.

4.1 Conventions

4.1.1 Baseline definition

Assessments performed at or shortly before the screening visit are considered as baseline. If more than one measurement of the same item satisfies this condition, the most recent measurement is considered as baseline. Collection of PBAC assessment was not included in protocol version V01. For subjects starting with protocol version V01, the first assessment under protocol version V02 serves as baseline.

4.1.2 Missing data

No imputations for missing data will be performed. Calculations pertaining to the derivation of annualized 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.

4.2 Demographic and other background data

The disposition of subjects (cf. Section 3) will be tabulated for the entire population. Details on important 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, ethnic group) will be summarized in tables and presented for the FAS population. Other baseline and background data as listed below will also be analyzed by descriptive tables (according to their type /continuous/categorical) for the FAS population:

- AB0 blood group (if available)
- Age at first treatment with VCP
- Family history of VWD
- History of VWD or FVIII inhibitors
- Available historical data on VWF activity obtained by VWF:RCo, VWF:Gp1bM, VWF:Gp1bR assays, or any other method and VWF:Ag as well as VWF multimer pattern for VWD type 2A, genotype for VWD type 2B,, VWF multimer pattern for VWD type 2A, and genotype for VWD type 2B
- Historical annual bleeding rate (ABR) calculated from number of bleeding episodes in the previous 6 months

- Hemophilia Joint Health Score (HJHS) at baseline
- QoL scales (PROMIS-29, SF-36; SF-10 for patients <16 years of age) at baseline
- Historical PBAC score

4.3 VCP exposure, compliance

The following parameters of VCP administrations will be documented:

- Name and batch number(s)
- Dates and times of injections
- Doses in IU and IU/kg
- Purpose of injection (treatment of BE, prophylaxis of recurrent bleeding, surgery, prophylaxis after surgery and other on-demand treatment)

Overall descriptive summaries will be provided for

- Number of Injections
- Number of Exposure Days
- Total Dose (IU)
- Dose (IU/kg)
- Dose (IU/kg) per exposure day
- Reason for Administration
- Overall period of exposure (from first- to last dose of VCP)

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

4.4 Medical history

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

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.

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). Concomitant medication tables will show the frequencies of subjects by WHO Drug Global preferred term.

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

4.6 Concomitant non-pharmacological measures, pre-medication

Not applicable.

4.7 Efficacy

The analysis of the efficacy of on-demand treatment with VCP will be based on the FAS and additionally on the PP set if these populations differ by >5%.

Primarily, all obtained data on treatment characteristics (VCP dosages, frequencies, total consumption) and BEs (site, type, duration, frequency, efficacy assessment) will be described by providing summary statistics.

For the efficacy analysis on bleeding episodes by site of bleeding a separate site category for 'Nose' will be generated. Assignment to this category will be based on the collected verbatim for 'Other site, specify' (e.g. Nose bleed, Epistaxis or similar meaning).
Bleeding episodes that are ongoing at screening visit but started prior to screening will be captured in study database and will be listed, but will be excluded from efficacy analysis.

4.7.1 Primary Endpoint

Primary endpoint of this study is to estimate the total annualized bleeding rate (TABR) during on-demand treatment with any VCP.

TABR will be calculated as the total number of spontaneous bleeds, traumatic bleeds and other bleeds in the time period between screening visit and the study completion visit, divided by the duration (in years) between first dose of VCP and the study completion visit. Surgery periods, and BEs occurring within these surgery periods, will be excluded from the calculation of TABR. Menstrual bleeds will not be included in this calculation, but reported and analyzed separately.

Descriptive statistics for TABR along with exploratory 95% Confidence Intervals will be presented.

4.7.2 Secondary Endpoints

Secondary endpoints are:

- Spontaneous annualized bleeding rate (SABR), calculated in analogy with TABR
- Data on the consumption of VCP product (VWF/FVIII IU/kg per month per patient) used for routine on-demand treatment

The following secondary efficacy endpoints will be studied except in Croatian centers:

- Effectiveness of VCP in the treatment of BEs based on the proportion of successfully treated BEs (definition see section 6.2)
- Effectiveness of surgical prophylaxis with VCP based on the proportion of successfully treated surgeries (definition see section 6.3)
- Pictorial Blood Loss Assessment Chart (PBAC) score

Regarding the VCP administration data, the following parameters will be documented:

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

Descriptive statistics will also be presented for the SABR and for time in study, exposure days, number of infusions and dosages of VCP overall and by reason for VCP injection.

Additionally, descriptive statistics will be presented for the traumatic annualized bleeding rate (TRABR), calculated in analogy with TABR.

4.7.3 Efficacy in surgical prophylaxis

The assessments will be performed only in non-Croatian centres.

Efficacy in surgical prophylaxis will be analyzed descriptively, presenting summary tables and listings 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
- Actual duration of surgical procedure
- Actual blood loss
- Pre-, intra-, and/or postoperative VCP administration data (only listed)
- Pre-, intra-, and postoperative FVIII and VWF:Rc plasma levels (only listed)
- Details on concomitantly administered products, except standard anesthetic products (only listed)
- Blood transfusion requirements (only listed)
- Assessment of efficacy of surgical prophylaxis at end of postoperative period by treating physician
- 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

For descriptive statistics on VCP consumption in context of surgeries by time point, all administrations documented under reason for treatment "Surgery" which have been administered before start of surgery will be considered as preoperative and administered between start and end of surgery as intraoperative treatments. Post-operative treatments will include all VCP treatments documented under reason for treatment "Prophylaxis after surgery".

4.7.4 Menstrual Bleedings (only female patients of childbearing potential)

For female patients, the results of the PBAC score over time will be summarized in descriptive tables for each complete menstrual cycle including changes to baseline.

Annualized rates of heavy menstrual bleedings will be calculated in analogy with TABR and summarized in descriptive tables. For the exploratory endpoint 'Annualized rate of heavy menstrual bleeds' descriptive statistics will be tabulated.

4.8 Safety

All safety analyses will be based on the FAS population.

The analysis of safety will include the occurrence of Adverse Drug Reactions and the occurrence of VWF/FVIII inhibitors.

4.8.1 Adverse Drug Reactions

Any adverse event (AE) which has a reasonable possibility of a causal relationship with the medicinal product will be considered as an Adverse Drug Reaction (ADR).

Adverse Drug Reactions (ADRs) will be coded by the Data Management of the CRO according to version stated in the DMP. Coding will be agreed upon with the Sponsor before database lock (cf. DMP).

All ADRs occurring after first VCP administration will be listed in appendix 16.2 of the report.

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

A descriptive analysis will be performed. Incidences will be presented by primary system organ classes (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 TEADRs irrespective of the causality assessment
- TEADRs by worst severity

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

- Serious ADRs (SADRs)
- ADRs which led to death
- ADRs which led to discontinuation

Serious non-treatment emergent ADRs will be listed separately.

4.8.2 Other relevant Safety data

Other relevant safety information is any information relating to:

- Pregnancies
- Drug abuse
- Misuse
- Overdose
- Medication errors
- Interactions with other medicinal products or devices
- Occupational exposure associated with any VCP used during this study, even if no ADR occurred

Any data obtained on the mentioned other safety information will be listed in individual patient listings.

4.9 Other variables

Not applicable.

4.10 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 planned 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 (SP). 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.)
Surgery Period	(Date of surgery – date of last VCP treatment for surgery + 1)/365.25
Total Annualized Bleeding Rate (TABR)	Number of bleedings excluding menstrual bleedings / (date of study completion – date of screening + 1)/365.25 (Surgery periods, and BEs occurring within these surgery periods, will be excluded from the calculation of TABR. BEs occurring at day of surgery but prior to start of surgery/start of treatment for surgery will be included into calculation)
Spontaneous Annualized Bleeding Rate (SABR)	Number of spontaneous bleedings / (date of study completion – date of screening + 1)/365.25 (Surgery periods, and BEs occurring within these surgery periods, will be excluded from the calculation of SABR. BEs occurring at day of surgery but prior to start of surgery/start of treatment for surgery will be included into calculation)
Traumatic Annualized Bleeding Rate (TRABR)	Number of spontaneous bleedings / (date of study completion – date of screening + 1)/365.25 (Surgery periods, and BEs occurring within these surgery periods, will be excluded from the calculation of TRABR. BEs occurring at day of surgery but prior to start of surgery/start of treatment for surgery will be included into calculation)
Heavy Menstrual Bleeding Rate (HMBR)	Number of heavy menstrual bleedings* / (date of study completion – date of screening + 1)/365.25 (* for a definition refer to section 6.4)
ED	Exposure day = each calendar day the subject received VCP

6.2 Algorithm for the Effectiveness of Treatment of BEs

The effectiveness will only be assessed in non-Croatian centres.

At the end of a BE (except for menstrual bleedings), treatment effectiveness will be assessed by the patient (together with the treating physician in case of on-site treatment) using the predefined criteria detailed in the table below.

Rating	Description
Excellent	Bleeding was completely stopped within 3 days in case of minor bleed, within 7 days in case of major bleed, and within 10 days in case of gastrointestinal bleed
Good	Bleeding was completely stopped, but time and/or dose slightly exceeded expectations
Moderate	Bleeding could be stopped only by significantly exceeding time and/or dose expectations
None	Bleeding could be stopped only by using other VCP

All effectiveness ratings assessed as either ‘excellent’ or ‘good’ will be considered ‘successfully treated’.

6.3 Algorithm for the Overall Efficacy Assessment for Surgical Prophylaxis

The effectiveness of surgical prophylaxis will only be assessed in non-Croatian centres.
The evaluation of overall effectiveness in surgeries will be made at the end of the postoperative period by the treating physician according to the following rules:

Rating	Description
Excellent	Haemostasis similar to that of a haemostatically normal patient
Good	Mildly abnormal haemostasis in terms of quantity and/or quality (e.g., slight oozing)
Moderate poor	Moderately abnormal haemostasis in terms of quantity and/or quality (e.g., moderate controllable bleeding)
None	Severely abnormal haemostasis in terms of quantity and/or quality (e.g., severe haemorrhage that is difficult to control)

All effectiveness ratings assessed as either 'excellent' or 'good' will be considered 'successfully treated'.

6.4 Criteria for Heavy Menstrual Bleeding

Any menstrual bleeding that meets any of the following criteria will be classified as Heavy Menstrual Bleeding for analysis purposes:

- Interferes with daily activities such as work, housework, exercise, or social activities,
- Requires changing pads/tampons more frequently than hourly (referred to as 'flooding',
- Lasts 7 or more days,
- Includes the presence of clots > 1 cm combined with a history of flooding,
- PBAC score ≥ 185, whenever PBAC score are applicable.

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 trial statistician and the statistical programmer 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.

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