Statistical Analysis Plan

Study ID	**WIL-20**
Study title	**Surveillance of Safety and Efficacy of wilate® in patients with von Willebrand disease**

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Supersedes document	**1.1**
Reason for change	Major changes in subgroup analysis. Exclusion of menstrual bleedings from bleeding analysis and adding new subgroup analysis to evaluate menstrual bleedings. New treatment categories assigned (Prevention and Menstruation). Further tables and listings added.

Protocol (version) this SAP is based upon	WIL-20 Study Protocol 03, 23.05.2012 (with amendment No. 2 incorporated) WIL-20 Study Protocol 04, 28.08.2012 (with amendment Nos. 2 and 3 incorporated) US country specific version

Purpose	The Statistical Analysis Plan describes the statistical analyses to be performed on surveillance WIL-20 in full detail, and the resulting output that will be compiled in a statistical report.
Scope	

Attachments

Approved by

Name and function Date and signature

[redacted]

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Glossary

Term	Description
ADR	Adverse Drug Reactions
ADQ	Additional Data Query
CM	Concomitant Medications
CRF	Case Report Form
CRO	Contract Research Organization
DBR	Database Release Meeting
DCF	Data Clarification Form
DD	D-Dimer
DDAVP	1-Deamino-8-D-Arginine Vasopressin
DOB	Date of Birth
DM	Data Manager/Data Management
DMP	Data Management Plan
DV(P)	Data Validation (Plan)
ED	Exposure Days
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
F1+2	Prothrombin Fragments 1 and 2
GCP	Good Clinical Practice
IU	International Unit
MedDRA	Medical Dictionary for Regulatory Activities
NTF	Note to File (specific regulations affecting the data processing)
QA(U)	Quality Assurance (Unit)
PUPs	Previously Untreated Patients
QC	Quality Control
SADR	Serious Adverse drug reaction
SAS	Statistical Analysis System
SOC	System Organ Class (WHO, MedDRA)
SOP	Standard Operating Procedure
TMF	Trial Master File
VWD	Von Willebrand Disease
VWF	Von Willebrand Factor
WHO	World Health Organization

1. Introduction / Objectives

1.1. Introduction

wilate® is a freeze-dried preparation consisting of the two active ingredients: human plasma-derived coagulation Factor VIII (FVIII) and von Willebrand Factor (VWF). It is used for the treatment and prophylaxis of bleedings in patients with haemophilia A and in the treatment and prophylaxis of bleeding in patients with von Willebrand disease, incl. major surgeries.
The hereditary form of von Willebrand's disease (VWD) is a common coagulation disorder with an estimated worldwide prevalence of 0.9-1.3%. Only a part of this patient population requires treatment, as there is great variability of geno- and phenotypes. The three main types of VWD are: type 1, 2 and 3. They are associated with quantitative (type 1 and 3) and qualitative defects (type 2) of the VWF. VWF/FVIII concentrates are administered mainly to patients with type 3, but patients with type 1 or 2 may also need regular or occasional substitution. Generally, the substitution frequency is very variable.
New biotechnological methods and chromatographic materials have been introduced in the development and production of wilate®. The result is a highly purified concentrate that contains FVIII/VWF complex in its natural form and in its physiological ratio of close to 1:1. wilate® is virtually free from low-molecular impurities.
wilate® is double virus-inactivated using the solvent/detergent method and a dry heating process (PermaHeat, 100°C for 2 hours).
wilate® has been shown to be efficacious and safe in the prophylaxis and treatment of bleeding, incl. major surgeries in patients with all types of VWD in several GCP-clinical trials [1].

This post-marketing surveillance is designed to ensure long-term consistency between data from the pre-licensure clinical studies (where by definition only a limited number of subjects is included) and routine clinical use. Documentation of the administration of wilate® in clinical practice will not only improve the efficacy and tolerability knowledge database, but will produce findings that cannot be obtained in the same way in controlled clinical studies. This surveillance will support the optimal use of wilate® thus bringing benefit for both physicians and patients.

1.2. Study Objectives

1.2.1. Primary objective

Primary objective is to document the safety and tolerability of wilate® in the treatment of acute bleeding, in the prophylaxis of VWD and in interventional procedures (e.g. minor/major surgery, dental care, invasive diagnostic procedures etc.).

1.2.2. Secondary objective(s)

Secondary objective is to document the efficacy of wilate® in the treatment of acute bleeding, in the prophylaxis of VWD and in interventional procedures (e.g. minor/major surgery, dental care, invasive diagnostic procedures etc.).

2. Design

This is open-label, prospective, multinational, post-marketing, non-interventional observational surveillance. The observation started in Q4 2010 and was planned to be completed after 5 years, with an individual observation period of 2 years.

3. Endpoints

3.1. Primary endpoint

Incidence of recorded adverse drug reactions (side effects) including thrombogenicity and immunogenicity and wilate® tolerability results assessed by a 3 point Verbal Rating Scale define primary endpoints.

3.2. Secondary endpoint

The secondary endpoint is defined as the percentage of the effectiveness ratings “excellent” and “good” based on a 4-point hemostatic efficacy scale applied in the treatment of acute bleeding, in the prophylaxis of VWD and in interventional procedures (e.g. minor/major surgery, dental care, invasive diagnostic procedures etc.).

4. Analysis Populations

4.1. Safety Population

All patients treated with at least one dosage of wilate® will be considered in the safety population.

4.2. Efficacy Populations

4.2.1. ITT Population

Due to the observational, non-interventional nature of the study, a differentiation of Intention-to-treat and per-protocol population will not be necessary. Therefore the ITT-population includes all patients of the safety population with confirmed VWD.

The following subpopulations of the ITT population are considered additionally:

- Routinely treated population (EFF):
  All subjects of the ITT population treated routinely* with wilate® (prophylactically, on demand or for surgical interventions)
- Surgery population (EFF-SURG):
  All patients of the EFF population with documented surgical intervention(s) for which
  - any amount of wilate® prior to, during or after the surgery is documented and
  - no other VWF or FVIII concentrate is documented within 72 hours prior to surgery

*The following patients will be excluded from the efficacy population:

- Patients under prophylactic treatment regimen that received prophylactic treatment for less than 3 month with no documented surgeries (reason for exclusion: insufficient data)
- Patients under on demand treatment regimen with no documented bleeding episodes, surgeries or menstrual bleedings (reason for exclusion: no treated/documented surgery, bleeding or menstruation under on demand regimen
- Patients significantly violating the In-/Exclusion criteria

5. Statistical Methods

5.1. General Presentation

The general presentation of the analysis will be according to the EMA-guideline 48663 [2].
All collected efficacy and safety assessments will be presented by means of descriptive statistics. If not detailed otherwise, the parameters listed below will be tabulated according to the different types of data. The number of subjects in the analysis population (N) and the number of subjects contributing to each particular summary (n) will be included in every presentation.

Where appropriate, results will be presented grouped by different subject characteristics, such as bleeding sites and severities or surgery categories, as well as in total.

- Binary data (whether or not an event has occurred): counts and proportions
- Count data (the frequency of an event in a set time period): rate (count per unit time)
- Continuous data (measurements on a continuous scale, including quasi-continuous variables): arithmetic mean, standard deviation, median, lower and upper quartile, minimum, maximum
- Scales data (Ordinal and Non-ordinal): absolute and relative frequencies
- When incidences are computed, these will always be in relation to all patients at risk in the associated analysis population (e.g. incidences of ADRs)

5.2. Statistical Concept

The statistical analysis of all endpoints will be performed descriptively. Additional descriptive and exploratory statistics, such as geometric means or confidence intervals, are included as appropriate. No confirmatory hypothesis testing is planned. When confidence intervals are computed, these will be two-sided 95% confidence intervals.

5.2.1. Efficacy Analysis

5.2.1.1. Efficacy in bleeding episodes (excluding menstrual bleedings)

The efficacy in treatment of bleeding episodes will be evaluated by descriptive statistics for the following parameters:

- Basic bleeding characteristics including site, cause and severity
- Total number and frequency of bleeding episodes (spontaneous, traumatic, other) during the study
- Frequency of bleeding episodes per year and month
- Overall efficacy rating per bleeding episode rated by patient and by investigator
- Frequency of successfully treated bleeding episodes (excellent and good efficacy rating, see also grouped efficacy in Appendix 1)
- The number of infusions needed to treat a BE, the number of EDs and study drug consumption data (wilate® IU/kg per infusion, per ED and BE) per subject and in total will be evaluated

5.2.1.2. Efficacy in menstrual bleeding episodes

- Bleeding characteristic severity
- Overall efficacy rating per menstrual bleeding rated by patient and by investigator
- Frequency of successfully treated menstrual bleedings (excellent and good efficacy rating, see also grouped efficacy in Appendix 1)
- The number of EDs and study drug consumption data per subject and in total will be evaluated

5.2.1.3. Efficacy in prophylactic treatment

The following parameters will be evaluated:

- The number of infusions, the number of EDs for prophylactic reason and study drug consumption data (wilate® IU/kg per infusion, wilate® IU/kg per month and year) per subject and in total will be evaluated
- Bleeding frequency in patients under continuous prophylaxis (see definition in Appendix 1)

5.2.1.4. Efficacy in surgeries

Efficacy in case of surgeries will be based on the following presentations:

- Number of subjects undergoing surgeries (minor, major, total)

- Number of surgeries by severity category (minor, major, total) and system organ class
- Details on treatment for surgical prophylaxis (number of exposure days and injections prior to surgery, dosing details, total amount of wilate®)
- Details on treatment with wilate® pre-, intra- and post-operatively (see Appendix 1) (number of exposure days and injections, dosing details, total amount of wilate®)
- Evaluation of blood loss and hematomas
- Use of blood and blood product transfusions
- Overall haemostatic efficacy evaluation at the end of surgical treatment period.
- FVIII plasma levels and VWF RCo activity in the context of the surgery

5.2.2. Safety Analysis

5.2.2.1. Adverse Drug Reactions (ADR)

All ADRs occurring after initiation of study treatments (including any undesirable sign, symptom, medical condition, or abnormal laboratory result) will be displayed in summary tables, listings and figures.

Incidences of ADRs will be given as numbers and percentages of subjects with:

- Any ADR by MedDRA System Organ Class (SOC)

Additionally, ADRs will be summarized by severity and relationship to study treatment.

All ADRs including MedDRA coded terms and the corresponding original (verbatim) terms will be listed in detail.

5.2.2.2. Tolerability assessments for prophylactic treatments and treatments of bleedings

For the presentation of the tolerability of wilate® summary tables will be generated:

- Tolerability evaluation per injection based on a three-point verbal rating scale by reason of administration and in total
- Number of excellent and good ratings per injection by reason of administration and in total

5.2.2.3. Immunogenicity

Provided that VWF antibody status or inhibitor activities have been determined antibody and inhibitor status and development will be represented by the following:

- Frequency of subjects with VWF antibodies and inhibitory VWF antibodies (inhibitors) at baseline and during study
- An estimate for the incidence rate of VWF antibodies and inhibitors will be calculated and presented together with two-sided 95% Pearson Clopper confidence intervals (tested negative on the first ED and tested positive during the course of the observation)

5.2.2.4. Thrombogenicity

Results of thrombogenicity markers will be tabulated per visit and all results listed individually. Statistics on changes of thrombogenicity markers between post-injection and pre-injection time points will be represented.

5.2.2.5. Antibody status

The following parameters will be evaluated:

- Antibody status of parvovirus B19, hepatitis C and HIV at baseline as well as antibody status of parvovirus B19 at each visit and study completion for all subjects
- An estimate for the incidence of seroconversions will be given together with 95% confidence intervals

5.2.2.6. Abnormal laboratory values

All documented laboratory values which are out of normal range will be listed including date of sampling and associated reference range taken from literature [3].

5.2.3. Other Analyses

5.2.3.1. Baseline characteristics

The following baseline characteristics will be displayed in full detail for all subjects:

- General demographic data
- VWD anamnesis
- Bleeding frequency at start of study
- Treatment of VWD before start of study
- Concomitant medication including associated MedDRA coded terms

5.2.3.2. Viral and vaccination status

The following parameters will be evaluated:

- Hepatitis A and B infections in the past
- Hepatitis A and B vaccinations in the past and at visits

5.2.3.3. Recovery

In case FVIII and VWF concentrations have been measured before and after wilate® injection, in-vivo recovery will be calculated based on actual potency and presented by means of descriptive statistics.

5.2.3.4. Laboratory Examinations

Summary tables of all laboratory examinations evaluated at baseline, follow up visits and surgeries will be presented if applicable, as well as listing of all measured laboratory parameters including normal ranges. In case no normal ranges are available these will be taken from literature [3].

5.2.3.5. Concomitant Medications (Diary)

Baseline medications, medications taken in context of a surgery and all other medications (diary) administered after the patient has started treatment with wilate® as well as changes in dosing and frequency of baseline medications will be listed in full detail, including category (Baseline, Surgery, Concomitant medication) and associated WHO drug dictionary coded terms.

5.2.3.6. Days out of school/work

- Total number of absent days and reason for absence will be presented
- Number of absent days in the past 6 months at baseline, number of absent days per 6-months intervals during the course of the surveillance will be calculated and corresponding differences will be investigated.

5.3. Interim Analysis

A first interim analysis will be performed upon sponsor's request. Further interim analyses will then be performed once a year until surveillance completion.

5.4. Subgroup Analyses

In addition to the analysis populations the following subgroups will be considered for selected aspects of the analysis.

5.4.1. Treatment regimen class/Treatment regimen

For each patient of the EFF population treatment regimen classes will be defined by the sponsor on the basis of available CRF data according to the following rules

- On demand:
  On demand treatment of bleeding episodes and menstrual bleedings
- Continuous prophylaxis:
  Continuous prophylaxis. Patients received continuous treatment over a period of at least 3 months with no gaps of treatment for longer than 14 days, or patients received continuous treatment for at least one year with an average of 1 infusion/per week (these patients may have gaps of more than 14 days)
- Intermittent prophylaxis:
  Intermittent prophylaxis. All prophylactically treated patients where the definition above does not apply
- Surgery only:
  Patients enrolled for treatment in context of interventional procedures only
- Mixed classes (e.g. Intermittent prophylaxis/On demand):
  Patients may change the treatment regimen from prophylaxis to on demand or vice versa.

For all subgroup analyses per treatment regimen patients with mixed regimen class will be included in both regiments, prophylactic and on demand regimen, respectively. For calculation of time under regiment see Appendix 1 (Transformations/Deviations).

5.4.2. Reason for administration - treatment category

The following treatment categories will be used for analysis of study drug consumption data:

- Bleeding: wilate® administered in context of bleeding episodes (except menstruation)
- Menstruation: wilate® administered in context of menstrual bleedings (category will be changed from 'Bleeding' to 'Menstruation' in analysis data)
- Prophylaxis: wilate® administered prophylactically for patients under prophylactic treatment regimen (continuous or intermittent)
- Prevention: wilate® administered 'prophylactically' for patients under 'On demand' or 'Surgery only' regimen, e.g. administered post-op or post bleeding (category will be changed from 'Prophylaxis' to 'Prevention' in analysis data)
- Thrombogenicity: wilate® administered at visit to determine thrombogenicity markers (Prothrombin fragments 1 + 2, D-dimers) or FVIII/VWF-concentrations

Treatments may be assigned to more than one category (will be analyzed for each category), e.g.:

- Prophylaxis + Thrombogenicity: For patients under prophylactic regimen all treatments administered for 'Thrombogenicity' will be additionally assigned to category 'Prophylaxis'
- Bleeding + Menstruation: A bleeding episode occurred simultaneously to menstrual bleeding

5.4.3. Surgeries

All data in the context of surgeries will be presented differentiated by category of surgery (minor /major) as outlined in section 5.2.1.4 and in section 2.2. of Appendix 2.

5.4.4. Menstrual bleedings

All menstrual bleedings will be excluded from efficacy analysis of other bleeding episodes. Efficacy assessment of menstrual bleedings and details on wilate® consumption will be analyzed separately. Menstrual bleedings will be identified via their cause specification ('monthly/ menstrual cycle or period, 'menorrhagia', 'menstruation, etc.). The reason for treatment for menstrual bleedings will be 'menstruation'. If a wilate® administration has been used to treat both, a menstrual bleeding and a bleeding with other cause, the reason will be 'bleeding + menstruation'.

5.5. Imputation of Missing Data

In general missing data values will not be completed apart from the following cases:

- Missing values which are authorized to be completed in accordance with the data handling rules defined in section 4.2.2 of the DMP (version 1.0)
- For the computation of dosages per kg body weight the last available weight (documented in context of thrombogenicity determination or changes in prophylactic dosing at visits) will be carried forward and used for the calculation (LOCF)
- If the completion date is missing the last available documented date will be used for the calculation of the study duration per patient (e.g. treatment date, date of laboratory sampling)

5.6. Software used

All statistical calculations and summary tables generated will be performed with the SAS-system, version 9.3 or higher.

6. Data Derivations and Data Transfer

The results of data transformations and derivations will be stored in analysis data sets and transferred to the sponsor upon completion of the final statistical analysis. All data transformations and derivations are listed in detail in Appendix 1.

7. Tables, Figures and Lists

An overview of the summary tables and illustrating figures to be included in the study report of this analysis and its appendix 14 is given in appendix 2 of this SAP.
Lists of all data recorded during the study will be presented in appendix 16.2 of the study report. A detailed overview of all planned lists is included in appendix 2 of this SAP.

8. Changes from Analyses Specified in the Protocol

No changes are planned to the analyses specified in the protocol.

9. References

Other documents	Description
Protocol	WIL-20 Study Protocol 03, 23.05.2012 (with amendment No.2 incorporated)

Other documents	Description
	WIL-20 Study Protocol 04, 28.08.2012 (with amendment No.2 and 3 incorporated) US country specific version
[1]	E. Berntorp, J. Windiga and the European Wilate Study Group; Treatment and prevention of acute bleedings in von Willebrand disease--efficacy and safety of Wilate, a new generation von Willebrand factor/factor VIII concentrate. Haemophilia. 2009 Jan;15(1):122-30
[2] Guideline	EMA/48663/2013 (30 July 2013): Guidance for the format and content of the final study report of non-interventional post-authorisation safety studies, Patients Health Protection, London
[3] Laboratory Normal Ranges	The Merck Manual. Normal laboratory values at http://www.merckmanuals.com (last reviewed/modified April 2013). Normal values F 1+2: Barthels, M., Poliwoda, H.: Gerinnungsanalysen, 6. Auflage; Page 339

Appendix 1 Transformations / Derivations

Item	Derivation
Annual and monthly bleeding rate	For patients with regimen 'continuous prophylaxis', the calculation of annual and monthly bleeding rate is based on the study duration.
Preceding inequality signs	For any statistic calculation preceding inequality signs (>, <) will be ignored
BW	Body weight (kg)
C_{max}	Maximum factor VIII level or VWF Ristocetin Co-factor activity or VWF antigen level (%), respectively, after end of IMP infusion
$C_{baseline}$	Baseline factor VIII level or VWF Ristocetin Co-factor activity or VWF antigen level (%), respectively, before start of IMP infusion
Dose used for recovery	Total dose of IMP administered based on actual potency (IU)
Dose	Nominal dose (IU)
Efficacy assessment for prophylaxis of bleedings	The efficacy of spontaneous breakthrough or traumatic bleedings will be evaluated based on the monthly bleeding rate as follows: *Excellent*: Less than 0.75 spontaneous or traumatic BE per month. *Good*: Between 0.75 and 1 spontaneous or traumatic BE per month. *Moderate*: Between 1 and 1.5 spontaneous or traumatic BEs per month. *Poor*: More than 1.5 spontaneous or traumatic BEs per month.
Grouped efficacy rating	Episodes with efficacy rating 'excellent' or 'good' and Episodes with efficacy rating 'moderate' or 'none
Intra-operative dose	Total dose of any injection documented as 'during procedure' by the investigator on the surgery CRF
In-vivo Recovery	= $(C_{max}-C_{baseline})$ * BW/dose. Results will be reported as %/(IU/kg).
On-demand treated patients*	Patients treated for bleedings, menstrual bleedings and study related investigations only. These patients may be treated for surgeries in addition
Prophylactically treated patients*	Prophylactically treated patients will be sub-classified into continuously and intermittently treated patients as defined below: *Continuous prophylaxis*: patients received continuous treatment over a period of at least 3 months with no gaps of treatment for longer than 14 days, or patients received continuous treatment for at least one year with an average of 1 infusion/per week (these patients may have gaps of more than 14 days) *Intermittent prophylaxis*: all prophylactically treated patients where the definition above doesn't apply.
Parvovirus B19 IgG seroconversion	In case of missing baseline test results the parvovirus B19 status will be set to negative at baseline
Post operative dose	Total dose of any injection given after the end of the surgery (end of surgery is defined as "last suture") which are documented as 'post-procedure' by the investigator on the surgery CRF
Preloading dose in surgery	The last total daily dose before start of surgery. In case that more than one day is documented as 'pre-procedure', only the closest day before surgery will be used for the calculation of preloading dose
Reason for administration	The reason for treatment of menstrual bleedings will be assigned to category 'MENSTRUATION' Prophylactic treatments for patients under treatment regiments 'On demand' or 'Surgery only' will be assigned to category 'PREVENTION'
Seroconversion/ Antibody/inhibitor development	baseline/entry result negative or unknown and at least 1 test at follow-up visits positive

Item	Derivation
Study duration	= last date - entry visit date +1. The last date will be either the completion or the final visit date, whichever occurred later or the last follow-up visit date for patients not completed
Surgery-only patients*	Patients enrolled for treatment in context of interventional procedures only.
Switch in regimen*	Patients may change the regimen from prophylaxis to on demand. For all subgroup analysis per treatment regimen these patients will be included in both classes, prophylactic and on demand class, respectively. Prophylactic phases for less than 3 months will be excluded from efficacy analysis.
Time under regimen	For all patients who did not change the treatment regimen during the observation the entry visit date and the last date* will be taken as start and end date of the treatment period. In case of a switch from prophylaxis to on demand regimen the start and end of the treatment period will be defined as followed: Prophylaxis: start = date of entry visit; end = date of last prophylactic treatment + 6 days wash-out On demand: start = end of prophylaxis (see above) + 1 day, end = last date* * The last date will be either the completion or the final visit date, whichever occurred later or the last follow-up visit date for patients not completed.
VWF antibody and inhibitor status	All results documented under 'Inhibitor testing (ELISA) on the CRF will be regarded as VWF antibody testing (test = VWF antibody). Tests for inhibitory activity of VWF antibodies (performed only for antibody positive samples) are not presented on CRF pages and will be taken from original laboratory sheets provided by central laboratory or from separate tables or DCF responses provided by Octapharma (see also data management NTF 03).
VWF antibody seroconversion/ Inhibitor development	In case of missing baseline test results the VWF antibody/ inhibitor status will be set to negative at baseline

* The final categorization will be decided by Octapharma during the data review meeting

Appendix 2 Tables, Figures and Lists details

Tables

All tables included will be represented for all patients as well as surgery-only patients. If indicated in description the efficacy (EFF) and efficacy surgery-population (EFF-SURG) will also be stratified by regimen class.

I*	T/F/L	Description	Popul.
Section 1 Demographic and other baseline data			
X		Definitions of populations and treatment regimens including abbreviations	NA
X	T	Subject analysis populations	All
X	T	Treatment regimen classes	EFF, EFF-SURG
X	T	Subject disposition	All
X	T	Gender distribution (by regimen class)	SAF, ITT, EFF, EFF-SURG
X	T	Distribution of ethnic origin (by regimen class)	SAF, ITT, EFF, EFF-SURG
X	T	Statistics on age, body height, body weight, body mass index (by regimen class)	SAF, ITT, EFF, EFF-SURG
X	T	General condition at baseline (‘good’, ‘not good’, frequency counts)	SAF, ITT, EFF, EFF-SURG
X	T	VWD type (frequency counts, by regimen class)	SAF, ITT, EFF, EFF-SURG
X	T	Statistics on age at screening, at diagnosis and time since diagnosis of VWD at screening (by regimen class)	SAF, ITT, EFF, EFF-SURG
X	T	Statistics on basal FVIII:C, VWF:RCO and VWF:Ag activities per VWD type (by regimen class)	SAF, ITT, EFF, EFF-SURG
X	T	Exposure days to FVIII/VWF containing products (0 (PUP), < 150 EDs, ≥ 150 EDs, frequency counts) (by regimen class)	SAF, ITT, EFF, EFF-SURG
	T	Number and frequency of previously treated patients (PTPs) and previously untreated patients (PUPs)	SAF, ITT, EFF, EFF-SURG
X	T	VWD anamnesis: history and gene mutation (by regimen class, frequency counts)	SAF, ITT, EFF, EFF-SURG
X	T	Response to DDAVP per VWD type (by regimen class, frequency counts)	SAF, ITT, EFF, EFF-SURG
X	T	Statistics on bleeding frequency per month at baseline by treatment regimen (and regimen class) (in the past)	SAF, ITT, EFF, EFF-SURG
X	T	Severity of bleedings in the past by VWD type (and regimen class)	SAF, ITT, EFF, EFF-SURG
	T	Product(s) for treatment of VWD in the past 6 months by VWD type (and regimen class) (frequency counts)	SAF, ITT, EFF, EFF-SURG
	T	Tolerability of previous treatment per VWD type (and regimen class) (frequency counts)	SAF, ITT, EFF, EFF-SURG
	T	Statistics on total consumption, number of exposures days to VWD products and days lost from school within the past 6 months before study entry by VWD type	SAF, ITT, EFF, EFF-SURG
X	T	Frequency of positive and negative Hepatitis C, HIV and Parvovirus B19 antibody results at baseline (by regimen class)	SAF, ITT, EFF, EFF-SURG
X	T	Frequency of hepatitis infections/vaccinations at baseline (by regimen class)	SAF, ITT, EFF, EFF-SURG

I*	T/F/L	Description	Popul.
X	T	Frequency of positive and negative VWF antibody and inhibitor results at first treatment (by regimen class)	SAF, ITT, EFF, EFF-SURG
Section 2 Efficacy data			
2.1	**Bleeding Episodes (without Menstrual Bleedings)**		
2.1.1	**Statistics on bleeding episodes**		
X	T	Number and frequency of bleeding episodes (per month and year under regimen) per patient	EFF
X	T	Number of patients with bleedings and number of bleeding episodes per treatment regimen	EFF
X	T	Number and frequency of bleeding episodes per cause and treatment regimen	EFF
X	T	Number and frequency of bleeding episodes per cause for treated and untreated episodes	EFF
	F	Frequency of bleeding episodes per treatment regimen and cause for treated and untreated episodes	EFF
X	T	Number and frequency of bleeding episodes per month and cause of bleeding for all episodes (all patients of the population and all patients under regimen)	EFF
X	T	Number and frequency of bleeding episodes per year and cause of bleeding for all episodes (all patients of the population and all patients under regimen)	EFF
X	T	Severity of bleeding episodes by treatment regimen and site of bleeding	EFF
X	T	Statistics on frequency of episodes (total number and rate per month and year, calculation base = patient) (by treatment regimen)	EFF
X	T	Statistics on average duration of episode and exposure days to wilate® per episode (calculation base = patient) (by treatment regimen)	EFF
X	T	Statistics on bleeding duration (days) per bleeding site and treatment regimen (calculation base = episodes)	EFF
X	T	Statistics on bleeding duration (days) by severity and treatment regimen (calculation base = episodes)	EFF
2.1.2	**Statistics on wilate® consumption for bleeding episodes and duration of treatment**		
X	T	Statistics on number of infusions per bleeding episode by treatment regimen and site for treated episodes (calculation base = episodes)	EFF
X	T	Statistics on number of infusions per bleeding episode by severity of bleeding and VWD type for treated episodes (calculation base = episodes)	EFF
X	T	Number of treated bleeding episodes stratified by treatment regimen and infusion category (1-2 or > 2 infusions, frequency counts)	EFF
X	T	Statistics on total dose (IU and IU/kg BW) per bleeding episode by treatment regimen and site for treated episodes (calculation base = episodes)	EFF
X	T	Statistics on total dose (IU and IU/kg BW) per bleeding episode by severity of bleeding and VWD type for treated episodes (calculation base = episodes)	EFF
X	T	Statistics on average daily dose (IU and IU/kg BW) per bleeding episode by treatment regimen and site for treated episodes (calculation base = episodes)	EFF
X	T	Statistics on average daily dose (IU and IU/kg BW) per bleeding	EFF

I*	T/F/L	Description	Popul.
		episode by severity of bleeding and VWD type for treated episodes (calculation base = episodes)	
X	T	Statistics on number of infusions per bleeding episode by site (and treatment regimen) for treated episodes (calculation base = patients)	EFF
X	T	Statistics on total dose (IU and IU/kg BW) per bleeding episode by site (and treatment regimen) for treated episodes (calculation base = patients)	EFF
X	T	Statistics on total dose (IU and IU/kg BW) per bleeding episode by severity of bleeding and VWD type for treated episodes (calculation base = patients)	EFF
X	T	Statistics on average daily dose (IU and IU/kg BW) per bleeding episode by site (and treatment regimen) for treated episodes (calculation base = patients)	EFF
X	T	Statistics on average daily dose (IU and IU/kg BW) per bleeding episode by severity of bleeding and VWD type for treated episodes (calculation base = patients)	EFF
X	T	Statistics on treatment duration (days) per bleeding site and treatment regimen for treated episodes (calculation base = episodes)	EFF
X	T	Treatment duration (days) for bleeding episodes per bleeding site by treatment regimen (frequency counts)	EFF
X	T	Treatment duration (days) for bleeding episodes by severity and treatment regimen (frequency counts)	EFF
2.1.3	**Efficacy assessment in treatment of bleeding episodes**		
X	T	Overall efficacy assessment by patient per bleeding site and treatment regimen for treated episodes (frequency counts)	EFF
	F	Overall efficacy assessment by patient per bleeding site and treatment regimen for treated episodes	EFF
X	T	Overall efficacy assessment by investigator per bleeding site and treatment regimen for treated episodes (frequency counts)	EFF
	F	Overall efficacy assessment by investigator per bleeding site and treatment regimen for treated episodes	EFF
X	T	Grouped efficacy assessment by patient per bleeding site and treatment regimen for treated episodes (frequency counts)	EFF
X	T	Grouped efficacy assessment by investigator per bleeding site and treatment regimen for treated episodes (frequency counts)	EFF
X	T	Overall efficacy assessment by patient per severity of bleeding and treatment regimen for treated episodes (frequency counts)	EFF
	F	Overall efficacy assessment by patient per severity of bleeding and treatment regimen for treated episodes	EFF
X	T	Overall efficacy assessment by investigator per severity of bleeding and treatment regimen for treated episodes (frequency counts)	EFF
	F	Overall efficacy assessment by investigator per severity of bleeding and treatment regimen for treated episodes	EFF
2.2	**Menstrual Bleedings**		
X	T	Number of patients with documented menstrual bleedings and number of menstrual bleedings	
X	T	Severity of menstrual bleedings (frequency counts)	
X	T	Statistics on total dose (IU and IU/kg BW) for menstrual bleedings by severity of bleeding and VWD type (calculation base = episodes)	
X	T	Statistics on total dose (IU and IU/kg BW) for menstrual bleedings by severity of bleeding and VWD type (calculation base = patients)	

I*	T/F/L	Description	Popul.
X	T	Statistics on treatment duration (days) for menstrual bleedings (calculation base = episodes)	
X		Treatment duration (days) for menstrual bleedings (frequency counts)	
X	T	Overall efficacy assessment in treatment of menstrual bleedings by patient and investigator per severity of bleeding (frequency counts)	
X		Grouped efficacy assessment in treatment of menstrual bleedings by patient and investigator per severity of bleeding (frequency counts)	
2.3	**Interventional Procedures**		
X	T	Frequency of interventional procedures per severity category (minor/major) and body system	EFF-SURG
X	T	Statistics on number of infusions and exposure days per procedure and severity category and in total	EFF-SURG
X	T	Statistics on number of infusions and exposure days per procedure, severity category, VWD type and in total	EFF-SURG
X	T	Statistics on wilate® consumption per infusion (total, relative dose) by severity category of procedure and VWD type (calculation base = infusions)	EFF-SURG
X	T	Statistics on total dose (IU and IU/kg BW) per procedure and severity category and in total	EFF-SURG
X	T	Statistics on total dose (IU and IU/kg BW) per procedure, severity category, VWD type and in total	EFF-SURG
X	T	Statistics on average daily dose (IU and IU/kg BW) per procedure and severity category and in total	EFF-SURG
X	T	Statistics on average daily dose (IU and IU/kg BW) per procedure, severity category, VWD type and in total	EFF-SURG
X	T	Statistics on total dose (IU and IU/kg BW) by severity category of procedure and infusion time point (calculation base = time point)	EFF-SURG
X	T	Statistics on average daily dose (IU and IU/kg BW) by severity category of procedure and infusion time point (calculation base = exposure days)	EFF-SURG
X	T	Total wilate® consumption by severity category of procedure (and infusion time point)	EFF-SURG
X	T	Total wilate consumption (number of infusions, exposure days, total and relative dose) by severity category and VWD type	EFF-SURG
X	L	Blood loss per time point – Listing	EFF-SURG
X	L	Blood products administered per time point – Listing	EFF-SURG
X	T	Overall hemostatic efficacy assessment by severity category of procedure and body system (frequency counts)	EFF-SURG
	F	Overall hemostatic efficacy by severity category of procedure	EFF-SURG
2.4	**Prophylaxis**		
2.4.1	**Statistics on wilate® consumption for prophylaxis**		
X	T	Statistics on number of exposure days and number of infusions for prophylactic treatments by treatment regimen (calculation base = patients)	EFF
X	T	Statistics on wilate® doses (IU and IU/kg BW) per infusion for prophylactic treatments by treatment regimen (calculation base = infusions)	EFF
X	T	Statistics on prophylactic wilate® infusions per week and month by treatment regimen (calculation base = patients)	EFF
X	T	Statistics on total wilate® consumption (IU and IU/kg BW) for	EFF

I*	T/F/L	Description	Popul.
		prophylactic treatments by treatment regimen (calculation base = patients)	
X	T	Statistics on wilate® consumption per week (IU and IU/kg BW) for prophylactic treatments by treatment regimen (calculation base = patients)	EFF
X	T	Statistics on wilate® consumption per month (IU and IU/kg BW) for prophylactic treatments by treatment regimen (calculation base = patients)	EFF
X	T	Statistics on wilate® consumption per year (IU and IU/kg BW) for prophylactic treatments by treatment regimen (calculation base = patients)	EFF
2.4.2	**Breakthrough bleedings under prophylaxis**		
X	T	Number of patients with breakthrough bleedings under prophylaxis by treatment regimen	EFF
X	T	Frequency of breakthrough bleedings per site and in total for patients under prophylaxis by treatment regimen (calculation base = episodes)	EFF
X	T	Frequency of breakthrough bleedings per site and in total for patients under prophylaxis by treatment regimen (calculation base = patients)	EFF
X	L	Number of bleedings per month and type for patients under continuous prophylactic treatment – Listing	EFF
X	T	Efficacy assessment in prevention of bleedings per type for patients under continuous prophylactic treatment inclusive totals (frequency counts)	EFF
2.5	**General**		
2.5.1	**wilate® consumption**		
X	T	Statistics on wilate® consumption per exposure day (total, relative dose) by treatment regimen and reason of administration (calculation base exposure days)	SAF, EFF
X	T	Statistics on wilate® consumption per exposure day (total, relative dose) by treatment regimen and reason of administration (calculation base patient)	SAF, EFF
X	T	Statistics on wilate® consumption per infusion (total, relative dose) by treatment regimen and reason of administration (calculation base = infusions)	SAF, EFF
X	T	Statistics on wilate® consumption per infusion (total, relative dose) by reason of administration and VWD type (calculation base = infusions)	SAF, EFF
X	T	Statistics on total wilate® consumption by treatment regimen (number of infusions, exposure days, total dose, calculation base = patients)	SAF, EFF
X	T	Total wilate® consumption (by treatment regimen)	SAF, ITT, EFF
2.5.2	**Completion/Termination / Overall efficacy**		
X	T	Termination of the surveillance by analysis population (frequency counts)	ALL
X	T	Overall efficacy assessment by treating physician and patient at final visit by VWD type	EFF
	F	Overall efficacy assessment by treating physician and patient at final visit by VWD type	EFF
X	T	Overall efficacy assessment by treating physician and patient at final	EFF

I*	T/F/L	Description	Popul.
		visit by regimen class	
	T	Statistics on bleeding frequency per month and total consumption, exposure days and days lost from school/work per 6-months before and during study)	EFF
2.5.3	**FVIII:C, VWF:RCo and VWF:Ag activities**		
X	L	FVIII:C, VWF:RCo and VWF:Ag activities at first treatment and during study - Listing	EFF
X	T	Statistics on FVIII:C, VWF:RCo and VWF:Ag at first treatment (by time point and VWD type)	EFF
Section 3 Safety data			
3.1	**Display of Adverse Events**		
X	T	Incidence of adverse drug reactions with 95% confidence limits	SAF
X	T	Incidence of adverse drug reactions in total, by system organ class (SOC) and preferred terms (PT)	SAF
3.2	**Listing of Deaths, Other Serious and Significant Adverse Events**		
X	T	Listing of serious adverse events (not available)	SAF
3.3	**Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events**		
X	T	Listing of narratives for serious adverse drug reactions or deaths (not applicable)	SAF
3.4	**Abnormal Laboratory Value Listing**		
X	T	Abnormal laboratory values at visits (Hematology) – Listing	SAF
X	T	Abnormal laboratory values at visit (Chemistry) – Listing	SAF
X	T	Thrombogenicity markers more than 2-fold above upper limit - Listing	SAF
X	T	Abnormal laboratory values at surgery – Listing	SAF
3.5	**Summaries of Laboratory Data and Other Safety Data**		
X	T	Frequency of parvovirus B19 IgG seroconversion with 95% confidence limits (baseline result negative and at least 1 test positive)	SAF
X	T	Frequency of VWF antibody and inhibitor development with 95% confidence limits (baseline result negative and at least 1 test positive)	SAF
X	T	Statistics on plasma levels of thrombogenicity markers F 1+2 and D-dimers during study (mean values per time point and differences to pre-injection levels)	SAF
	F	Statistics on changes of thrombogenicity markers F 1+2 and D-dimers between post-injection and pre-injection time points (box blot)	SAF
X	T	Tolerability assessment of each wilate® injection by reason for administration (prophylactic treatment and treatment of bleedings, frequency counts)	SAF
X	T	Tolerability assessment of each wilate® injection by reason for administration (prophylactic treatment, treatment of bleedings and treatments in context of a surgery, frequency counts)	SAF

*: X =To be included in interim (I) analysis
T/F/L=Tables/Figures/Lists

Lists

Interim*	Description	
X		Definitions of populations and treatment regimens including abbreviations
1	**Discontinued Patients**	
X	L	Discontinued patients (incl. time in study and number of EDs)
2	**Protocol Deviations**	
X	L	Violated in-/exclusion criteria
X	L	Protocol deviations (if applicable)
3	**Patients Excluded from the Analysis**	
X	L	Patients excluded from safety analysis
X	L	Patients excluded from efficacy analysis
X	L	Disposition of subjects with respect to analysis populations
4	**Demographic Data and Other Baseline Data**	
X	L	Subject demographics
X	L	General condition at baseline
X	L	Von Willebrand disease anamnesis
X	L	Age at entry, at diagnosis and time since diagnosis of VWD at screening
X	L	FVIII:C, VWF:RCo and VWF:Ag activity at baseline
X	L	Current bleeding frequency (in the past)
X	L	Current treatment of VWD (in the past 6 months)
X	L	Days missed from school or work /in the past 6 months
X	L	Viral/antibody status at baseline
X	L	Concomitant medication at baseline
5	**Compliance and/or Drug Concentration Data**	
X	L	Batch numbers used
6	**Individual Efficacy Response Data**	
6.1	**General efficacy response data**	
X	L	Patients time profile
X	L	wilate® doses during study including reason for administration) and tolerability
X	L	First and last treatment, time in study, number of exposure days, number of infusions and wilate® consumption per day
X	L	Completion information
X	L	Overall efficacy assessment of treatment with wilate® by treating physician and patient at final visit/completion
6.2	**Bleeding episodes**	
X	L	Bleeding episodes (except menstrual bleedings)
X	L	Menstrual bleedings
X	L	Duration of bleeding episode, number of treatments, exposure days, total dose and average daily dose per bleeding episode
X	L	Duration of menstrual bleeding, number of treatments, exposure days, total dose and average daily dose per menstrual bleeding
6.3	**Interventional procedures**	
X	L	Description of the interventional procedure and procedure outcome
X	L	wilate® doses in the course of the interventional procedure

Interim*	Description	
X	L	Number of treatments, exposure days, total dose and average daily dose per interventional procedure
X	L	Evaluation of blood loss (incl. volume collected by drainage system and hematomas)
X	L	Blood products administered in the course of interventional procedures
X	L	Overall hemostatic efficacy assessment of wilate® (interventional procedures)
7	**Adverse Drug Reactions Listing**	
X	L	Adverse drug reactions
8	**Listing of Individual Laboratory Measurements by Patient**	
X	L	Laboratory examinations (hematology, chemistry) at baseline, visits and completion
X	L	Laboratory examinations at surgery - Hematology
X	L	Laboratory examinations at surgery - Chemistry (Liver and kidney function / enzymes)
X	L	Laboratory examinations at surgery - Chemistry (Electrolytes)
X	L	Laboratory examinations at surgery (and related wilate® administrations) – Coagulation
X	L	Laboratory examinations at surgery - VWF antibody
X	L	Antibody status parvovirus B19 at baseline, visits and completion
X	L	VWF antibody testing at first treatment and visits
X	L	VWF inhibitor testing at first treatment and visits
X	L	Thrombogenicity determination (F 1+2, D-dimers) at first treatment and during study
X	L	Thrombogenicity determination (F 1+2, D-dimers) - local laboratory
X	L	FVIII:C, VWF:RCo and VWF:Ag activity at baseline and during study (local laboratory)
X	L	Laboratory values from local laboratories documented elsewhere
X	L	IgG and IgM antibody results for Parvovirus B19
9	**Other Safety Data and Additional Information**	
X	L	Vaccination status (hepatitis A/B) at baseline and visits
X	L	Concomitant medication at baseline and during study (including medications in the context of interventional procedures)
X	L	Days out of school/work (incl. reason for absence)
X	L	Comments and other information of the investigator
X	L	Remarks of the investigator

*X=To be included in interim analysis
T/F/L=Tables/Figures/Lists