STATISTICAL ANALYSIS PLAN

Protocol No: WIL-27

Version Number: 5.0 Date of Issue: 2018-05-08	Page 1 of 27

Sponsor:	Octapharma AG
Title of Protocol:	Clinical Study to Investigate the Pharmacokinetics, Efficacy, Safety, and Immunogenicity of *Wilate* in Previously Treated Subjects with Severe Hemophilia A
Protocol Version/Date:	Version 05 / 2017-09-07
CRF Version:	Version 5.0 / 2017-08-11
Supersedes SAP Version:	Version 4.0

Document authorization

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[redacted]

Consistency check with the Protocol (one option to be selected)

[X] This is to confirm that as part of the SAP finalization consistency check with the current protocol / protocol amendment was performed by the trial statistician, and no changes to the protocol (statistical section) are required

[ ] Changes to the analysis principles were required, and the responsible team has confirmed commitment to update the study protocol

[ ] Changes to the analysis principles were required (as outlined in revision history section of this SAP), however it was not feasible to update the study protocol, for the reason

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Change control

Date	Author	Reason	Version
2016-09-22	[redacted]	Final Version	1.0
2016-11-14		Changes in SAP according to changes in study protocol as specified in Protocol Amendment #1, 2016-11-14	2.0
2017-01-16		Changes in SAP according to changes in study protocol as specified in Protocol Amendment #2, 2017-01-16	3.0
2017-10-02		Changes in SAP according to changes in study protocol as specified in Protocol Version 05, 2017-09-07	4.0
2018-05-08		Age subgroup definition changed upon sponsors request. Section 8.1: Definition for annual bleeding rate modified. Definition for prophylactic treatment phase added	5.0

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LIST OF ABBREVIATIONS

Abbreviation	Description
ABR	Annual Bleeding Rate
AE	Adverse Event
ANOVA	Analysis of Variance
AUC	Area Under the Curve
AUC_{norm}	AUC normalized for the administered dose
AUMC	Area Under the Moment Curve
BE	Bleeding Episode
BMI	Body Mass Index
BW	Body Weight
CD4	Cluster of Differentiation 4
CHR	Chromogenic assay
CI	Confidence Interval
CL	Clearance
C_{max}	Maximum Plasma Concentration
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DD	Drug Dictionary (WHO Coding Thesaurus)
DBR	Database Review
DMP	Data Management Plan
DVP	Data Validation Plan
ED	Exposure Day
EDC	Electronic Data Capture
EOT	End of Trial
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FVIII	Coagulation Factor VIII
FVIII:C	Factor VIII-coagulant

Abbreviation	Description
HJHS	Hemophilia Joint Health Score
ICF	Informed Consent Form
ID	Identifier
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention-To-Treat
IU	International Unit
IV	Intravenous
IVR	Incremental in Vivo Recovery
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean Residence Time
N	Number of Subjects/Observations
OS	One-stage assay
PK	Pharmacokinetic
POP	Postoperative
PP	Per-Protocol
PT	Preferred Term
PTP	Previously Treated Subject
QC	Quality Control
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software package
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SABR	Spontaneous Annualized Bleeding Rate
SURG	Surgery analysis set

Abbreviation	Description
$T_{1/2}$	In Vivo Half-Life
TABR	Total Annualized Bleeding Rate
TEAE	Treatment Emergent Adverse Event
TLFs	Tables, Listings, Figures
T_{max}	Time to Reach Maximum Plasma Concentration
TS	Trial Statistician
Vd	Volume of distribution
VWD	Von Willebrand Disease
VWF	Von Willebrand Factor
VWF:Ac	VWF activity
VWF:Ag	Von Willebrand Factor Antigen
WHO	World Health Organization

1 STUDY MATERIAL

The following material was considered for this SAP:

Document	Version, Date
Protocol, incl. last amendment	2017-09-07, including Amendments #1 (2016-11-14), #2 (2017-01-16), #04 (2017-09-07)
CRF	TBD
DMP	TBD
DVP	TBD

2 STUDY INFORMATION

2.1 Primary objective

The primary objective of this study is to determine the efficacy of *Wilate* in the prophylactic treatment of previously treated subjects (PTP) with severe hemophilia A.

2.2 Secondary objective

The secondary objectives of this study are to:

- Determine the efficacy of *Wilate* in the treatment of breakthrough bleeding episodes (BEs)
- Calculate the FVIII:C pharmacokinetics (PK) for *Wilate* at baseline and after 6 months of prophylactic treatment
- Calculate the FVIII:C incremental IVR of *Wilate* over time (at baseline, and at 3 and 6 months of treatment)
- Assess the association between AB0 blood type and the FVIII:C half-life of *Wilate*
- Assess the association between the VWF:Ag concentration and the FVIII:C half-life of *Wilate*
- Assess the safety and tolerability of *Wilate*
- Assess the immunogenicity of *Wilate*

2.3 Additional Objective:

An additional objective of this study is the descriptive efficacy of *Wilate* in surgical prophylaxis.

2.4 Study design

This study is designed as a prospective, international, multi-center phase 3 study. Further details are given in the overview below:

FLOW CHART FOR PK ASSESSMENT AND PROPHYLACTIC TREATMENT
Part I

	Screen-ing Visit	PK Patients PK Visit	Non-PK Patients Non-PK Visit	Day-14 Visit (14-21 days)	Day-30 Visit (±3 days)	3-Month Visit (±2 weeks)
Informed consent	x					
Inclusion and exclusion criteria	x					
Demographics	x					
Weight	x	x [1]	x [1]			x [1]
Height	x					
Medical history (incl. FVIII treatment 6 months before screening)	x					
Vital signs	x	x [2]	x [4]			x [4]
Physical examination	x					
Routine safety laboratory	x	x [3]	x [4]			x [1]
Determination of CD4+ levels [8]	x					
Determination of AB0 blood group [9]	x					
HJHS, unless obtained within 3 months before screen-ing	x					
PK injection (50 ± 5 IU/kg)		x				
Blood sampling for FVIII:C (OS and CHR) for PK as-sessment		x [5]				
IVR injection			x [10]			x
Blood sampling for FVIII:C IVR (OS and CHR)			x [6]			x [6]
Factor VIII inhibitor [11]	x	x [1]	x [1]	x [1]	x [1]	x [1]
VWF:Ag and VWF:Ac		x [6]	x [6]	x [1]	x [1]	x [6]
Parvovirus B19 antibodies		x [1]	x [1]			
Retention sample for possible virus marker testing		x [1]	x [1]			
Patient diary review				x	x	x
Adverse event monitoring		x	x	»	»	»
Concomitant medications	x	»	»	»	»	»

PK = pharmacokinetic, IVR = in vivo recovery, HJHS = Hemophilia Joint Health Score, OS = one-stage assay, CHR = chromogenic assay, VWF:Ag = von Willebrand factor antigen, VWF:Ac = VWF activity

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Part II

	PK Patients	Non-PK Patients	
	PK Study Completion Visit at 6 months (+2 weeks)	Non-PK Study Completion Visit at 6 months (+2 weeks)	Follow-up Contact 30 days (±3 days) after Study Completion Visit
Informed consent			
Inclusion and exclusion criteria			
Demographics			
Weight	x [1]	x [1]	
Height			
Medical history (incl. FVIII treatment 6 months before screening)			
Vital signs	x [2]	x [4]	
Physical examination	x	x	
Routine safety laboratory	x [3]	x [4]	
Determination of CD4+ levels [8]			
Determination of AB0 blood group [9]			
HJHS, unless obtained within 3 months before screening			
PK injection (50 ± 5 IU/kg)	x		
Blood sampling for FVIII:C (OS and CHR) for PK assessment	x [5]		
IVR injection		x	
Blood sampling for FVIII:C IVR (OS and CHR)		x [6]	
Factor VIII inhibitor [11]	x [1]	x [1]	
VWF:Ag and VWF:Ac	x [6]	x [6]	
Parvovirus B19 antibodies	x [7]	x [7]	
Retention sample for possible virus marker testing			
Patient diary review	x	x	
Adverse event monitoring	x	x	x [12]
Concomitant medications	x	x	

[1] Before injection

[2] Before injection as well as 1 h (±5 min) and 48±2 h after injection

[3] Before injection as well as 48±2 h after injection **[local laboratory]**

[4] Before injection as well as 15±5 min after injection

[5] Blood sampling within 1 h before injection and 15±5 min, 1 h (±5 min), 3 h (±15 min), 6 h (±30 min), 9±1 h, 24±2 h, 30±2 h, and 48±2 h after end of injection **[central laboratory]**

[6] Blood sampling within 1 h before injection as well as 15±5 min after the end of injection **[central laboratory]**

[7] If first sample was negative for parvovirus B19 antibodies (sample to be taken before injection) **[central laboratory]**

[8] CD4+ count to be repeated if interval between Screening Visit and first injection exceeds 30 days. To be included into the study, the patient's CD4+ count must be >200/µL (i.e., inclusion criterion no. 4).

[9] Unless obtainable from patient's medical history

[10] First prophylactic injection

[11] Blood sampling for inhibitor testing should preferably be done at the time of trough FVIII:C levels **[central laboratory]**
In case of positive inhibitor results, inhibitor retesting using a second, separately drawn sample should be performed, preferably within 15 days of becoming aware of the positive result.

[12] Documentation of AEs potentially related to thromboembolic events only

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FLOW CHART OF ASSESSMENTS FOR SURGICAL PROPHYLAXIS

	Within 12 hours before start	Within 3 hours before start	Surgery		POP day 1	Any POP day	End of POP period [1]	3-8 weeks after surgery
			Intra-operatively	End				
Body weight	x							
Type of surgery	x							
Location of surgery	x							
Severity of surgery	x							
Expected duration of surgery	x							
Expected average/ maximum blood loss during surgery	x							
Actual duration of surgery				x				
Actual blood loss during surgery				x				
Administration of IMP		x	(x)	(x)	(x)	(x)	(x)	
FVIII plasma levels		#	(#)	(#)	# [2]	#	#	
VWF:Ag and VWF:Ac		#			# [2]	#	#	
Presence of wound hematomas					x	x	x	
Routine safety laboratory	x				(x)	(x)	(x)	
Vital signs	x		x		x			
Efficacy assessment				S			H	
Overall efficacy assessment							I	
FVIII inhibitor								x
Narrative of outcome							x	
Concomitant medications	throughout observation period							
Adverse event monitoring	throughout observation period							

POP, postoperative, VWF:Ag = von Willebrand factor antigen, VWF:Ac = VWF activity
( ) Optional
Samples to be taken immediately before (≤ 30 min) and 30±15 min after IMP administration
[1] Time immediately after the last surgical suture
[2] For major surgery, mandatory for the first 3 postoperative doses
S, performed by surgeon; H, performed by hematologist; I performed by Investigator

2.5 Planned sample size

55 male subjects with severe hemophilia A (<1% FVIII:C) aged ≥12 years with at least 150 previous exposure days (EDs) to a FVIII concentrate will be enrolled to obtain evaluable data on 50 subjects who complete 6 months of prophylactic treatment. Of these 50 subjects, 20 subjects will undergo two 2-day PK Assessment Phases of 1 dose of 50 IU ± 5 IU *Wilate*/kg body weight (BW) before the start and after the end of the Prophylactic Treatment Phase. Of the 20 patients undergoing the PK assessment, a minimum of 4 patients should be between ≥12 and <17 years of age.

No statistical sample size estimation was performed. The chosen sample size of 50 evaluable subjects will, however, be sufficient to reject the null hypothesis of a mean TABR >29 with

a power of >90% if the mean TABR is not greater than 20 BEs per person year with a maximum standard deviation of 15.

3 GENERAL INFORMATION

3.1 Background details

The data will be transferred to SAS from the Clinical Data Management System OPVERDI via a validated procedure. If applicable external data will also be transferred to SAS for presentation of these data in the statistical analyses.

3.2 Deviations from the trial protocol with regard to statistical analyses

No deviations from the protocol are planned.

3.3 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 therefore will lead to exclusion from particular analysis populations).

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

Criteria for major 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.

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 (DBR). 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. A description of all major protocol violations will be included in the table part of the CSR.

4 ANALYSIS POPULATIONS

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

- Safety (SAF) population
- Full Analysis Set (FAS)
- Per-Protocol (PP) population
- Pharmacokinetic (PK) set

- Surgery (SURG) set

4.1 Safety population

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

4.2 Full analysis set population

The **full analysis set (FAS)** defined according to the intention-to-treat (ITT) principle will include all enrolled subjects who received at least one infusion of IMP after the initial PK or at Non-PK Visit.

4.3 Per-protocol population

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 DBR).

4.4 Pharmacokinetic population

The **pharmacokinetic (PK) set** will include all subjects for which at least one valid *Wilate* PK profile has been obtained.

4.5 Surgery population

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

4.6 Subgroup analyses

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

- Age ('<16 years' and '≥16 years')
- Race ('American Indian or Alaska Native,' 'Asian,' 'Black or African American,' 'Native Hawaiian or Other Pacific Islander,' 'White,' 'Other');
- Geographical region ('patients in the US,' 'patients outside the US ');

Analysis of PK parameters will be presented by age ('< 16 years' and '≥16 years').

5 STATISTICAL ANALYSES

All statistical analyses will be performed using SAS® for Windows (Version 9.3 or later).

Descriptive statistics will always be given for the entire population.

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

The evaluation of the primary endpoint will be performed on the FAS (ITT analysis) and on the PP set (PP analysis).

For secondary endpoints, ITT and PP analyses will be carried out, unless these analysis sets differ by no more than 5% of subjects in the FAS.

Analysis of the PK properties of *Wilate* will be based on the PK set.

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. Usually mean and quartiles will have 1 decimal more, SD 2 decimals more than the original values (as given with min, max); N has no decimals. 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 1 or 2 decimals, as applicable. 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). Statistical significance will be declared if the rounded p-value will be less than 0.050.

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. '27-01-01'. Any derived data listed will also be stored permanently and will be calculated as outlined in section 8.1 of this SAP.

5.1 Conventions

5.1.1 Baseline definition

Assessments at screening visit or the first IVR measurement (at PK or Non-PK visit, respectively) are considered as baseline.

5.1.2 Missing data

In case of missing 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 PK or IVR 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.

5.1.3 Pooling of centers

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

5.2 Demographic and other background data

5.2.1 Basic description

The disposition of subjects (cf. Section 4) will be tabulated for the entire population. Details on protocol deviations will be listed.

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

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

- Blood group
- VWF:Ag, VWF:Ac and CD4+ levels at baseline
- FVIII inhibitor level
- Vital Signs (Systolic and diastolic blood pressure, pulse and body temperature) at screening
- Physical examination (normal/abnormal)
- Hemophilia joint health score (HJHS)
- Results of Parvovirus B19 antibodies
- Previous annual bleeding rate (ABR) calculated from number of bleeding episodes during the past 6 months documented under Medical history

The following background data will only be listed:

- Medical history (including FVIII treatment during the last 6 months before screening)

- Concomitant Medication

5.3 IMP exposure, compliance

Treatment will be administered prophylactically as defined in the protocol. Each treatment will be recorded in the diary along with the reason for treatment (prophylaxis, bleeding, prevention of recurrent bleeding, prophylaxis after surgery or other reason) and transferred to the CRF. Treatments in context of IVR measurements and surgeries will be documented in the eCRF only.

All IMP treatment details will be listed.

5.4 Medical history

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

5.5 Concomitant medication

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

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

Medications will be coded using the WHO DD thesaurus in the version current at the time of database lock. 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 DD preferred term. Prior medication will only be listed.

5.6 Concomitant non-pharmacological measures, pre-medication

Not applicable.

5.7 Efficacy

The analysis of the efficacy of prophylactic treatment with *Wilate* will be based on the FAS and the PP set.

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.

5.7.1 Primary endpoint

The primary endpoint of this study is a 50% reduction of the total annualized bleeding rate (TABR) observed in the GENA-01 study with a total of 58.1 BEs per subject per year.

The efficacy of prophylactic treatment with *Wilate* will be statistically evaluated by comparing the primary endpoint, i.e., TABR under prophylaxis, with a predefined threshold of 29 per subject per year. This threshold corresponds to 50% of the TABR reported in GENA-01, a study in which previously treated adolescent and adult subjects with severe hemophilia A received on-demand FVIII treatment only.

TABR will be calculated as the total number of BEs in the time period between first dose of IMP and the Study Completion Visit, divided by the duration (in years) between first dose of IMP and the Study Completion Visit. Surgery periods, and BEs occurring within these periods, will be excluded from the calculation of TABR.

A confirmative one-sided, one-sample Poisson-test will be used to test whether the mean TABR in subjects treated prophylactically with *Wilate* is below the threshold of 29 BEs per subject year (alpha = 2.5%). A corresponding two-sided 95% CI for the TABR will also be provided.

If μ denotes the mean TABR, then the following pair of hypotheses will be tested:

$$H_0: \mu \geq 29 \text{ vs. } H_1: \mu < 29$$

The null hypothesis will be rejected (at a one-sided alpha level of 2.5%) if the upper limit of the one-sided 97.5% confidence interval for μ is strictly less than 29.

This mentioned confidence interval will be derived from a generalized linear model with a Poisson error, log-link function and log (exposure time) as offset term.

5.7.2 Secondary endpoints

All secondary efficacy variables will be analyzed based on the FAS and additionally on the PP population if these populations differ by >5%. In case of surgical endpoints, the analysis will be based on the SURG set (refer to section 5.9) and for PK parameters on the PK set (refer to section 5.8).

Secondary endpoints are:

- Spontaneous annualized bleeding rate (SABR), calculated in analogy with TABR
- Efficacy of *Wilate* in the treatment of breakthrough BEs based on the proportion of BEs successfully treated with *Wilate* (successfully includes efficacy ratings assessed as either 'excellent' or 'good')
- *Wilate* consumption data (FVIII IU/kg per week per subject) for prophylaxis
- Baseline PK parameters for FVIII:C using both the chromogenic (CHR) and one-stage (OS) assays and actual IMP potencies (for details see section 5.8)

- Incremental IVR of *Wilate* over time (at baseline, and at 3 and 6 months of treatment)
- Association between AB0 blood type and the FVIII:C half-life of *Wilate*
- Association between VWF:Ag concentration and the FVIII:C half-life of *Wilate*
- Safety and tolerability of *Wilate* by monitoring adverse events (AEs) throughout the study (for details see section 5.10.1)
- Immunogenicity of *Wilate* by testing for FVIII inhibitors (for details see section 5.10.3)
- Virus safety in terms of parvovirus B19 (for details see section 5.10.3)

The secondary endpoint SABR will be analyzed in complete analogy to the TABR, the only exception being that, for the comparison of mean SABRs, a predefined threshold of 19.1 per subject per year is chosen; this threshold corresponds to 50% of the SABR reported in GENA-01.

If μ' denotes the mean SABR, then the following pair of hypotheses will be tested:

$$H_0: \mu' \geq 19.1 \text{ vs. } H_1: \mu' < 19.1$$

In addition to the comparison of the subjects' ABR to the defined thresholds derived from GENA-01, intra-individual comparisons with each subject's documented pre-study ABR (based on bleedings documented for at least 6 months prior to study start) will be performed. For this, descriptive statistics for pre-study and current ABRs and their intra-individual differences will be presented, and the matched-pairs signed rank test (alpha = 5%) will be used to test for a shift in ABR distributions.

Regarding efficacy in the treatment of breakthrough BEs, confirmatory statistical testing will test the null hypotheses that the percentage of success is ≤70% (alternative hypothesis: percentage >70%); the test procedure based on the generalized estimation equation will take into account several BEs in one subject as correlated repeated measurements.

Thus, if π denotes the proportion of success, then the following pair of hypotheses will be tested:

$$H_0: \pi \leq 0.7 \text{ vs. } H_1: \pi > 0.7$$

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

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

5.7.3 Exploratory Endpoint

An exploratory endpoint of this study is the descriptive efficacy of ***Wilate*** in surgical prophylaxis (for details see section 5.9).

5.8 Pharmacokinetics / Pharmacodynamics

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

The PK profiles of *Wilate* and the PK parameters derived from them will be summarized by descriptive statistics as well as the presentation of concentration vs. time plots based on the PK set. In the analysis of the PK profiles geometric means and standard deviations will be presented in addition to the arithmetic means and standard deviations.

The following PK parameter will be derived and presented using a non-compartment model:

- Area under the curve (AUC) and AUC normalized for the administered dose (AUC_{norm})
- FVIII in vivo half-life ($T_{1/2}$)
- Maximum plasma concentration (C_{max})
- Time to reach maximum plasma concentration (T_{max})
- Mean residence time (MRT)
- Volume of distribution (Vd)
- Clearance (CL)
- Incremental in vivo recovery (IVR)

Analysis of variance (ANOVA) will be used in an exploratory sense to assess a possible association between AB0 blood type, VWF:Ag, and the FVIII:C half-life of *Wilate*.

IVR will be analyzed for the FAS and additionally for the PP population if these populations differ by >5%. The results of the IVR assessments over time will be analyzed in summary tables for each time point and their differences to baseline along with 95% CIs for the mean differences.

To compare the pharmacokinetic characteristics of the 6-months PK-profile with those of the baseline PK-profile a matched-pairs sign rank test of the null hypothesis of no time difference will be performed at for all PK parameters.

5.9 Surgeries

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:

- Number of minor and major surgeries

- Location, severity (minor or major, for definitions see protocol), and type (planned or emergency) of surgery
- Expected and actual duration of surgical procedure
- Expected and actual blood loss
- Pre-, intra-, and/or postoperative IMP administration data (only listed)
- Pre-, intra-, and postoperative FVIII plasma levels (only listed)
- VWF:Ag and VWF:Ac (descriptive statistics including changes to pre-infusion)
- Presence of wound hematomas and whether or not they require surgical evacuation (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 taking both the intra- and postoperative assessments into account assessed by the Investigator.
- Number of successively treated surgeries ('excellent' or 'good' overall efficacy rating)
- Concomitantly administered products (only listed)
- Narrative describing the outcome and efficacy of the intervention (only listed)
- Inhibitor testing (within 3–8 weeks after the end of the surgery, this visit may coincide with another study visit with scheduled inhibitor testing)

5.10 Safety

All safety analyses will be based on the SAF population.

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.

5.10.1 Adverse events

Adverse events (AEs) will be coded by the CRO according to Medical Dictionary for Regulatory Activities (MedDRA) version 20.0. Coding will be agreed upon with the Sponsor before database lock (cf. DMP).

All adverse events recorded since signing of the informed consent form (ICF) will be listed in appendix 16.2 of the report differentiating by treatment emergent and non-treatment emergent events. This includes also post-study serious adverse events (SAEs) which occurred up to 4 weeks after the last IMP administration (not monitored proactively), thromboembolic events monitored proactively by performing a Follow-up Contact 30 days after the completion visit as well as safety relevant information on drug overdosing, drug interactions and medication errors.

The analysis will include only treatment-emergent adverse events (TEAEs), i.e. all documented AEs that started or worsened after the start of 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 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 TEAE irrespective of the causality assessment
- Related TEAEs ('Probably' or 'Possible')
- 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.

5.10.2 Vital signs

Vital signs parameters (systolic/diastolic blood pressure, pulse, body weight, respiratory rates, body temperature) will be assessed at screening, PK/Non-PK visit, after 3 months at study completion visits (PK and Non-PK) and during surgery.

Descriptive analyses of values will be performed and changes from baseline will be analyzed for vital signs parameters at visits.

5.10.3 Safety laboratory variables

The analysis of the safety parameters (lab values for Hematology and Clinical chemistry) recorded during visits (screening, PK or Non-PK visit, 3-month and study completion visits (PK and Non-PK)) 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 at each time point. Additionally, frequency tables for values outside the normal ranges will be presented.

Similarly, time profiles of 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. For the analysis of the inhibitor rate, in order to achieve a total number of at least 80 PTPs, data from this study will be pooled with those from previously completed clinical studies with *Wilate*.

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

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

5.10.4 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.

5.11 Other variables

Not applicable.

5.12 Interim analyses

Not applicable.

6 QUALITY CONTROL

The responsible project manager will review the SAP before it is provided to the Sponsor for review. The SAP will be signed off only when approval from the Sponsor's representative is received.

Log files of all SAS® programs needed for 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 author.

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.

7 REFERENCES

No specific references were used.

8 APPENDICES

8.1 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.)
Annual bleeding rate	Number of bleedings under prophylaxis / time under prophylaxis (days)/365.25 (see prophylactic treatment phase)
AUC	Area under the curve from baseline to infinity $AUC = \sum\left(\frac{(C_n + C_{n+1})}{2} \cdot \Delta t \right) + \frac{C_{last}}{K}$ (C_{last} is the last available measurement)
AUC_{norm}	AUC normalized for the administered dose
AUMC	Area under the moment curve (from baseline to infinity) $AUMC = \sum\left(\frac{(t_n \cdot C_n + t_{n+1} C_{n+1})}{2} \cdot \Delta t \right) + \frac{C_{last}}{K^2} + \frac{t_{last} \cdot C_{last}}{K}$
CL	Clearance $CL = \frac{D}{AUC}$ where D is the actual dose administered (see remark above)
C_0	FVIII concentration before IPM administration
C_{max}	Maximal measured concentration after end of IMP infusion (peak concentration)
ED	Exposure day = each day the subject received IMP
Incremental recovery (IVR)	$IVR = \frac{(C_{max} - C_0) \cdot BW}{D}$

	where BW stands for the body weight in kg and D is the dose according to the actual potency of the FVIII concentrate as described in above
MRT	Mean residence time $MRT = \frac{AUMC}{AUC}$
Prophylactic treatment phase	PK subgroup: (date of completion visit or date of last treatment with IMP in case completion visit not performed) – (date of first prophylactic treatment after the PK visit) Non-PK subgroup: (date of completion visit or date of last treatment with IMP in case completion visit not performed) – (date of first IMP infusion at Non-PK visit)
Success (for bleeding episodes and surgeries)	Excellent or good efficacy rating
$T_{1/2}$	In vivo half-life using linear regression on the terminal phase of the logarithm of the concentration; $T_{1/2} = \frac{\ln(2)}{K}$ (where *K,* the elimination rate constant, is determined as the slope of the regression line)
T_{max}	Time to reach maximum plasma concentration (Timing starts at end of infusion)
Vd	Volume of distribution $Vd = CL \cdot MRT$

8.2 Guide for assessment of overall efficacy for surgeries

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	Good	Moderate	None	None

8.3 List of Tables, Listings, Figures

A complete lists 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 includes the totality of statistical output to be produced. Therefore, this list will be approved by both parties before commencing the statistical programming.

All output will be headed with an appropriate heading specifying the study ID and abbreviated study title.

All output will be dated and have 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.

All statistical output will identify the underlying analysis populations and indicate the number of subjects / events in this population (N) and the number of subject/events actually contributing to the particular output (n). All statistical output will be presented per treatment group and in total (if applicable).

All subject listings will contain additionally to the subject identification the analysis population and the treatment group.