# CLINICAL STUDY PROTOCOL

## CLINICAL STUDY TO INVESTIGATE THE PHARMACOKINETICS, EFFICACY, SAFETY, AND IMMUNOGENICITY OF WILATE IN PREVIOUSLY TREATED PEDIATRIC PATIENTS WITH SEVERE HEMOPHILIA A

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| **Investigational Product:** | ***Wilate*** |
| **Indication:** | Severe hemophilia A (<1% FVIII:C) |
| **Study Design:** | Prospective, non-controlled, international, multi-center phase 3 study |
| **Sponsor:** | **Octapharma AG** [redacted] |
| **Study Number:** | WIL-30 |
| **EudraCT Number:** | 2017-001531-40 |
| **IND Number:** | IND 17181 |
| **Development Phase:** | Phase 3 |
| **Planned Clinical Start:** | Q4 2017 |
| **Planned Clinical End:** | Q3 2018 |
| **Date of Protocol:** | 19-Jun-2017 |
| **Version:** | 02, for Ukraine only |
| **Co-ordinating Investigator:** | [redacted] |

# STUDY OUTLINE

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| **Name of Sponsor/Company:**<br>Octapharma AG | |
| **Name of Investigational Product:**<br>Wilate | **Protocol Identification Code:**<br>WIL-30 |
| **Name of Active Ingredient:**<br>Factor VIII/VWF concentrate human | **Date of Final Protocol:**<br>19-Jun-2017 |

**Title of Study:** Clinical Study to Investigate the Pharmacokinetics, Efficacy, Safety, and Immunogenicity of *Wilate* in Previously Treated Pediatric Patients with Severe Hemophilia A

**Indication:** Severe hemophilia A (<1% FVIII:C)

**Number of Study Center(s):** Approximately 5 sites in Europe

**Objectives:**

***Primary Objective:***

The primary objective of this study is to determine the FVIII:C pharmacokinetics (PK) for *Wilate* in previously treated patients (PTP) with severe hemophilia A aged 1 to <12 years.

***Secondary Objectives:***

The secondary objectives of this study are to:

- Determine the efficacy of *Wilate* in prophylactic treatment
- Determine the efficacy of *Wilate* in the treatment of breakthrough bleeding episodes (BEs)
- 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*

***Additional Objective:***

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

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**Study Design:**

Prospective, non-controlled, international, multi-center phase 3 study

**Number of Patients:**

Overall, 10 PTPs (5 patients aged 1 to <6 years of age and 5 patients aged 6 to <12 years) will be enrolled into this study. The aim is to obtain evaluable data on 8 patients who complete both the 2-day PK Phase and the 6-month Prophylactic Treatment Phase. Of the 8 evaluable patients, 4 patients must be 1 to <6 years of age, and another 4 patients must be 6 to <12 years of age. Enrolled patients will be replaced only if they do not complete the PK assessment.

**Patient Selection Criteria:**

***Inclusion Criteria:***

1. Severe hemophilia A (<1% FVIII:C) according to medical history
2. Male patients aged 1 to <12 years
3. Previous treatment with a FVIII concentrate for at least 50 exposure days (EDs)
4. Immunocompetence (CD4+ count >200/µL)
5. Voluntarily given, fully informed written and signed consent obtained by the patient's parent(s) or legal guardian and, depending on the children's developmental stage and intellectual capacity, informed assent by the patients before any study-related procedures are performed

The interval between the Screening Visit and the PK Visit **should not exceed 30 days**. If the 30-day interval is exceeded, determination of the CD4+ count is to be repeated and must be >200/µL for patients to be enrolled (i.e., inclusion criterion no. 4).

***Exclusion Criteria:***

1. Any coagulation disorders other than hemophilia A
2. History of FVIII inhibitor activity (≥0.6 BU) or detectable FVIII inhibitory antibodies (≥0.6 BU using the Nijmegen modification of the Bethesda assay) at screening, as determined by the central laboratory
3. Severe liver or kidney diseases (alanine aminotransferase [ALAT] and aspartate transaminase [ASAT] levels >5 times of upper limit of normal, creatinine >120 µmol/L)
4. Patients receiving or scheduled to receive immunomodulating drugs (other than antiretroviral chemotherapy), such as alpha-interferon, prednisone (equivalent to >10 mg/day), or similar drugs

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5. Treatment with any investigational medicinal product in another interventional clinical study currently or within 4 weeks before enrollment
6. Hemoglobin level < 9 g/dL at the Screening Visit

**Test Product, Dose, and Mode of Administration:**

The factor VIII/VWF concentrate *Wilate*, produced from the plasma of human donors, is presented as a powder and solvent for intravenous injection containing nominally 500 IU or 1000 IU human von Willebrand factor (VWF) and human FVIII per vial.

***PK Assessment***

Single dose of 50 ± 5 IU kg BW.

***Prophylactic Treatment***

*Wilate* should be administered every 2 to 3 days at a dose of 20–40 IU/kg BW for 6 months. In case of unacceptably frequent spontaneous breakthrough BEs (i.e., more than 2 spontaneous BEs or 1 major or life-threatening spontaneous BE within a 30-day period), the dose of *Wilate* should be increased by approximately 5 IU/kg (depending on the entire content of the additional vial(s) that need(s) to be reconstituted).

Alternative prophylactic regimens at the discretion of the Investigator are also acceptable.

***Treatment of Breakthrough BEs***

- **Early hemarthrosis, muscle bleeding or oral bleeding**
  Target FVIII level: 20–40%
  Recommended dose: 10–20 IU/kg
  Repeat every 12–24 hours. At least 1 day, until the BE as indicated by pain has resolved or healing has been achieved.
- **More extensive hemarthrosis, muscle bleeding or hematoma**
  Target FVIII level: 30–60%
  Recommended dose: 15–30 IU/kg
  Repeat injection every 12–24 hours for 3 to 4 days or more until pain and disability have resolved.
- **Life-threatening hemorrhages**
  Target FVIII level: 60–100%
  Recommended dose: 30–50 IU/kg
  Repeat injection every 8–24 hours until threat has resolved.

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***Surgical Prophylaxis***

- **Minor surgeries, including tooth extractions**
  Target FVIII level: 30–60%
  Recommended dose: 15–30 IU/kg
  Every 24 hours, at least 1 day, until healing is achieved.
- **Major surgeries**
  Target FVIII level: 80–100% (pre- and postoperative)
  Recommended dose: 40–50 IU/kg
  Repeat injection every 8–24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a FVIII activity of 30% to 60%.

**Duration of Treatment:**

The planned duration of treatment for an individual patient is about 6 months (+2 weeks) and at least 50 EDs, plus a Follow-up Contact 30 days after the Study Completion Visit.

**Reference Therapy, Dose, Mode of Administration:** None

**Primary and Secondary Endpoints:**

***Primary Endpoint***

The primary endpoint of this study is the PK profile of *Wilate.*

***Secondary Endpoints***

The secondary endpoints of this study are the:

1. Total annualized bleeding rate (TABR)
2. Spontaneous annualized bleeding rate (SABR)
3. Efficacy of *Wilate* in the treatment of breakthrough BEs based on the proportion of BEs successfully treated with *Wilate*
4. *Wilate* consumption data (FVIII IU/kg per week per patient) for prophylaxis
5. Incremental IVR of *Wilate* over time (at baseline, and at 3 and 6 months of treatment)
6. Association between AB0 blood type and the FVIII:C half-life of *Wilate*
7. Association between VWF:Ag concentration and the FVIII:C half-life of *Wilate*
8. Safety and tolerability of *Wilate* by monitoring adverse events (AEs) throughout the study
9. Immunogenicity of *Wilate* by testing for FVIII inhibitors
10. Virus safety in terms of parvovirus B19

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***Exploratory Endpoint***

An exploratory endpoint of this study is the descriptive efficacy of *Wilate* in surgical prophylaxis.

**Study Outcome Parameters:**

***PK Parameters***

The following PK parameters will be assessed (FVIII:C using both the chromogenic (CHR) and one-stage (OS) assays and actual IMP potencies):

- Area under the curve (AUC) and AUC normalized for the administered dose ($AUC_{norm}$)
- 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)

***Efficacy Parameters***

*Prophylactic Treatment*

Efficacy of prophylactic treatment will be assessed based on the TABR, i.e., the total number of BEs per patient per year. The number of spontaneous BEs per patient per year (SABR) will also be used to assess prophylactic treatment efficacy.

*Treatment of Breakthrough BEs*

At the end of a BE, treatment efficacy will be assessed by the patient (together with the Investigator in case of on-site treatment) using the predefined criteria ‘excellent,’ ‘good,’ ‘moderate,’ and ‘none’.

The **proportion of BEs successfully treated with IMP** will be evaluated for all BEs taken together and by BE severity. All efficacy ratings assessed as either ‘excellent’ or ‘good’ will be considered ‘successfully treated.’

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*Surgical Prophylaxis*

Efficacy will be assessed at the end of surgery by the surgeon and at end of the postoperative period by the hematologist. In both cases, predefined assessment criteria will be used. In addition, the Investigator will assess the overall efficacy combining both the intra- and postoperative assessments.

***Safety Parameters***

Any of the following drug safety information shall be collected:

- Adverse events (AEs) and serious adverse events (SAEs) temporally associated with the administration of IMP
- Drug overdose, interaction, medication error, and post-study SAEs

*Central Laboratory*

The following laboratory tests will be done at the central laboratory:

- **FVIII:C** in the vials used for PK injections as well as in plasma using the CHR and OS assays
- **FVIII inhibitor activity** will be determined at each study visit before the injection of *Wilate* using the modified Bethesda assay (Nijmegen modification). Blood sampling for inhibitor testing should preferably be performed at the time of trough FVIII:C levels.

  If inhibitor development is suspected between study visits (e.g., based on an unexplained need to increase the dose, lack of efficacy of IMP injections, or prolonged bleeding), additional FVIII inhibitor tests will be performed and documented.

  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. If inhibitor development is confirmed by the second sample analyzed in the central laboratory, patients with low-titer inhibitors (<5 BU) may continue treatment with *Wilate*, while patients with high-titer inhibitors will be discontinued from the study.
- **VWF:Ag** and **VWF:Ac** will be measured at prespecified time points.
- **Virus safety** will be evaluated by taking a plasma sample for parvovirus B19 antibody testing during the Screening Visit. All patients negative during screening will be tested again at the Study Completion Visit.

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Retention serum sample for possible virus marker testing will be taken during the Screening Visit and stored at the central laboratory.

*Local Laboratory*

The following laboratory tests will be done by the local laboratories of each study site:

- **Hematology:** red blood cell count, white blood cell count, hemoglobin, hematocrit, and platelet count
- **Chemistry:** total bilirubin, alanine amino transferase, aspartate transaminase, blood urea nitrogen, serum creatinine
- **CD4+ count**
- **AB0 blood type**, unless known from medical history

**Study Procedures by Visit:**

***Screening Visit***

The following assessments will be performed:

- Obtaining voluntarily given, written (signed and dated) informed consent
- Inclusion and exclusion criteria
- Demographic characteristics
- Weight
- Height
- Medical history (including FVIII treatment during the last 6 months before screening)
- Vital signs
- Physical examination
- Hemophilia Joint Health Score (HJHS), unless obtained within 3 months before the Screening Visit
- Blood sampling for the following purposes:
  - Routine safety laboratory
  - Determination of CD4+ levels
  - Determination of AB0 blood group (unless derived from medical history)
  - Determination of FVIII inhibitors
  - Testing for parvovirus B19 antibodies
  - Retention sample for possible additional virus marker testing
- Concomitant medications

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The interval between the Screening Visit and the PK Visit **should not exceed 30 days**. If the 30-day interval is exceeded, determination of the CD4+ count is to be repeated and must be >200/µL for patients to be enrolled (i.e., inclusion criterion no. 4).

Any BEs occurring between the Screening Visit and the PK Visit should be treated with the patient's previously used FVIII concentrate. Similarly, prophylactic treatment between the Screening Visit and the PK Visit should be done with the patient's previously used FVIII concentrate.

***PK Visit***

Patients will receive *Wilate* at a dose of 50 ± 5 IU/kg (labelled dose) after a washout period of at least 72 hours from their last FVIII injection. Patients must not be experiencing any bleeding.

The following assessments will be performed:

- **Body weight** before injection
- Blood samples will be taken for the following purposes and at the following time points:
  - **FVIII:C plasma concentration (OS and CHR) for PK assessment** within 1 h before injection and 15±5 min, 1 h (±5 min), 6 h (±30 min), 24±2 h, and 48±2 h after the end of injection
  - **Safety laboratory** before and 48±2 h after injection
  - **FVIII inhibitor** before injection
  - Plasma **VWF:Ag** and **VWF:Ac** within 1 h before injection and 15±5 min after the end of injection
- **Vital signs** before injection as well as 1 h (±5 min) and 48±2 h after injection
- **AE monitoring**
- **Concomitant medications**

At the end of this visit, patients will **receive a patient diary**. The Investigator will explain to the patient how to fill in the diary and emphasize the importance of carefully documenting all treatment details, AEs, and concomitant medications. Also, patients will be **provided with IMP** for home treatment. They will be re-supplied whenever necessary during the study.

**The first prophylactic injection of *Wilate* after the PK Visit marks the beginning of the Prophylactic Treatment Phase.**

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***Day-14 Visit***

The Day-14 Visit will take place 14–21 days after the start of the Prophylactic Treatment Phase, if possible after a washout period of at least 48 hours from the patient's latest FVIII injection. The following assessments will be performed:

- Review of **patient diary**
- Blood samples will be taken for the following purposes and at the following time points:
  - **FVIII inhibitor** before injection
  - Plasma **VWF:Ag** and **VWF:Ac** before injection
- **AE monitoring**
- **Concomitant medication**

***Day-30 Visit***

The Day-30 Visit will take place 30±3 days after the start of the Prophylactic Treatment Phase, if possible after a washout period of at least 48 hours from the patient's latest FVIII injection. The assessments performed will be the same as for the Day-14 Visit.

***3-Month Visit***

The 3-Month Visit will take place 3 months (±2 weeks) after the start of the Prophylactic Treatment Phase.

A prophylactic injection of *Wilate* will be administered, if possible after a washout period of at least 48 hours from the patient's latest FVIII injection. Patients must not be experiencing any bleeding.

The following assessments will be performed:

- **Review of patient diary**
- **Body weight** before injection
- Blood samples will be taken for the following purposes and at the following time points:
  - **FVIII:C plasma concentration (OS and CHR) for IVR assessment** within 1 h before and 15±5 min after the end of the injection
  - **Safety laboratory** before injection
  - **FVIII inhibitor** before injection
  - Plasma **VWF:Ag** and **VWF:Ac** within 1 h before injection and 15±5 min after the end of injection

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- **Vital signs** before and 15±5 min after the end of injection
- **AE monitoring**
- **Concomitant medication**

***Study Completion Visit***

The Study Completion Visit will take place 6 months (+2 weeks) after the start of the Prophylactic Treatment Phase.

A prophylactic injection of *Wilate* will be administered, if possible after a washout period of at least 48 hours from the patient's latest FVIII injection. Patients must not be experiencing any bleeding.

The following assessments will be performed:

- **Review of patient diary**
- **Body weight** before injection
- Blood samples will be taken for the following purposes and at the following time points:
  - **FVIII:C plasma concentration (OS and CHR) for IVR assessment** within 1 h before injection of the last prophylactic dose and 15±5 min after the end of the injection
  - **Safety laboratory** before and 15±5 minutes after injection
  - **FVIII inhibitor** before injection
  - Plasma **VWF:Ag** and **VWF:Ac** within 1 h before injection and 15±5 min after the end of injection
  - **Parvovirus B19 antibodies** before injection, if first sample was negative
- **Vital signs** before and 15±5 min after the end of injection
- **AE monitoring**
- **Concomitant medication**
- **Physical examination**

All used and unused IMP vials will be returned by the patient.

Patients prematurely withdrawing from the study for any reason will also be invited to attend the Study Completion Visit.

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***Follow-up Contact 30 days after Study Completion Visit***

The purpose of the Follow-up Contact 30 days after the 6-month Study Completion Visit is to **document any thromboembolic events**, whether or not they are suspected to be related to study treatment.

The Follow-up Contact may either take the form of a personal visit by the patient to the study site or a telephone call by the Investigator. Any relevant AEs are to be recorded on the AE page of the eCRF.

***Unscheduled Visits and Additional Measures***

If inhibitor development is suspected (e.g., based on an unexplained need to increase the dose, lack of efficacy of IMP injections, or prolonged bleeding), FVIII inhibitor tests in addition to those scheduled during study visits will be performed and documented.

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. If inhibitor development is confirmed by the second sample analyzed in the central laboratory, patients with low-titer inhibitors (<5 BU) may continue treatment with *Wilate*, while patients with high-titer inhibitors will be discontinued from the study.

Other reasons for unscheduled visits may be the occurrence of serious AEs or hospitalizations because of severe BEs or because of a surgical intervention.

***Surgical Visits***

Patients may undergo surgical interventions in the course of the study. Whether or not patients undergoing surgeries will be hospitalized will depend on the type and severity of the surgery and be at the discretion of the Investigator. In patients undergoing major surgeries, standard methods of postsurgical thromboprophylaxis, such as gradated compression stockings and early mobilization, should be used to prevent venous thromboembolism.

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**Statistical Analysis Plan:**

The primary approach to the statistical analysis will be descriptive, presenting sampling statistics (n, mean, standard deviation, quartiles, and range) for continuous measurements and absolute and relative frequency counts for categorical/ordinal data. This will be complemented by exploratory confidence intervals (CIs) for means or proportions.

***Pharmacokinetic Analysis***

The PK profiles of *Wilate* and the associated PK parameters will be summarized by descriptive statistics as well as the presentation of concentration vs. time plots. Similarly, the results of the IVR assessments over time will also be analyzed in summary tables for each time point and their differences to baseline, along with 95% CIs for the mean differences. 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*.

***Efficacy Analysis***

Primarily, all obtained data on treatment characteristics (IMP dosages, frequencies, total consumption) and BEs (duration, frequency, efficacy assessment) will be described using above summary statistics.

*Efficacy of Prophylactic Treatment with Wilate*

The efficacy of prophylactic treatment with *Wilate* will be statistically evaluated by presenting descriptive sampling statistics for the TABR and SABR.

*Efficacy in the Treatment of Breakthrough BEs*

To assess the hemostatic efficacy of *Wilate* in the treatment of breakthrough bleedings, a frequency distribution of all such BEs being successfully treated will be presented, along with an exploratory 95% CI. The statistical analysis of other secondary endpoints will be descriptive, including exploratory 95% CIs for the location parameters.

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***Safety Analysis***

The analysis of safety will be based on the occurrence of AEs, the results of the safety laboratory tests, immunogenicity measurements, and the occurrence of parvovirus B19 seroconversions. Analysis of AEs will focus on treatment-emergent adverse events (TEAEs). Patient listings will be provided for patients with SAEs, AEs leading to withdrawal from study, and AEs leading to death.

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. Incidences of parvovirus B19 seroconversions between screening and end of study will be estimated along with 95% Pearson-Clopper CIs.

Other safety parameters (e.g., changes in physical examination findings) will be analyzed by summary tables or listings. The analysis of the safety parameters recorded during surgery (laboratory values) will be descriptive.

## FLOW CHART FOR PK ASSESSMENT AND PROPHYLACTIC TREATMENT

| | For details, see Section | Screening Visit | PK Visit | Prophylactic Treatment Phase (starts with first prophylactic injection of *Wilate* after the PK Visit) | | | | Follow-up Contact 30 (±3) days after Study Completion Visit |
|---|---|---|---|---|---|---|---|---|
| | | | | Day-14 Visit (14–21 days) | Day-30 Visit (±3 days) | 3-Month Visit (±2 weeks) | Study Completion (6-Month) Visit at 6 months (+2 weeks) | |
| **Informed consent** | | x | | | | | | |
| **Inclusion and exclusion criteria** | 4.1 | x | | | | | | |
| **Demographics** | 7.1.1 | x | | | | | | |
| **Weight** | | x | x [1] | | | x [1] | x [1] | |
| **Height** | | x | | | | | | |
| **Medical history (incl. FVIII treatment 6 months before screening)** | 7.1.2 | x | | | | | | |
| **Vital signs** | 7.3.6 | x | x [2] | | | x [4] | x [4] | |
| **Physical examination** | 7.3.6 | x | | | | | x | |
| **Routine safety laboratory** | 7.3.5 | x | x [3] | | | x [1] | x [4] | |
| **Determination of CD4+ levels [8]** | 7.1.1 | x | | | | | | |
| **Determination of AB0 blood group [9]** | 7.1.1 | x | | | | | | |
| **HJHS, unless obtained within 3 months before screening** | 7.1.1 | x | | | | | | |
| **PK injection (50 ± 5 IU/kg)** | | | x | | | | | |
| Blood sampling for FVIII:C (OS and CHR) for PK assessment | 7.3.5 | | x [5] | | | | | |
| **IVR injection** | | | | | | x | x | |
| Blood sampling for FVIII:C IVR (OS and CHR) | 7.3.5 | | | | | x [6] | x [6] | |
| **Factor VIII inhibitor [10]** | 7.3.5 | x | x [1] | x [1] | x [1] | x [1] | x [1] | |
| **VWF:Ag and VWF:Ac** | 7.3.5 | | x [6] | x [1] | x [1] | x [6] | x [6] | |
| **Parvovirus B19 antibodies** | 7.3.5 | x | | | | | x [7] | |
| **Retention sample for possible virus marker testing** | 7.3.5 | x | | | | | | |
| **Patient diary review** | | | | x | x | x | x | |
| **Adverse event monitoring** | 7.3 | | x | » | » | » | x | x [11] |
| **Concomitant medications** | 7.1.2 | x | » | » | » | » | 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.

## LEGEND TO THE FLOW CHART FOR PK ASSESSMENT AND PROPHYLACTIC TREATMENT

**[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), 6 h (±30 min), 24±2 h, and 48±2 h after the 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]** 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.

**[11]** Documentation of any thromboembolic events only (to be documented on AE page)

## FLOW CHART OF ASSESSMENTS FOR SURGICAL PROPHYLAXIS

| | For details, see Section | Within 12 hours before start | Within 3 hours before start | Surgery | | POP day 1 | Any POP day | End of POP period | 3-8 weeks after surgery |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Intra-operatively | End [1] | | | | |
| **Body weight** | | x | | | | | | | |
| **Type of surgery** | | x | | | | | | | |
| **Location of surgery** | | x | | | | | | | |
| **Severity of surgery** | 7.2.5 | x | | | | | | | |
| **Expected duration of surgery** | | x | | | | | | | |
| **Expected average/ maximum blood loss during surgery** | 7.2.5 | x | | | | | | | |
| **Actual duration of surgery** | | | | | x | | | | |
| **Actual blood loss during surgery** | | | | | x | | | | |
| **Administration of IMP** | | | x | (x) | (x) | (x) | (x) | (x) | |
| **FVIII plasma levels** | 7.2.5 | | # | (#) | (#) | (#) [2] | (#) | (#) | |
| **VWF:Ag and VWF:Ac** | 7.3.5 | | # | | | (#) [2] | (#) | (#) | |
| **Presence of wound hematomas** | | | | | | x | x | x | |
| **Routine safety laboratory** | 7.3.5 | x | | | | (x) | (x) | (x) | |
| **Vital signs** | 7.3.6 | x | | x | | x | | | |
| **Efficacy assessment** | 7.2.6 | | | | S | | | H | |
| **Overall efficacy assessment** | 7.2.6 | | | | | | | I | |
| **Factor VIII inhibitor [3]** | 7.3.5 | | | | | | | | x |
| **Narrative of outcome** | | | | | | | | x | |
| **Concomitant medications** | | throughout observation period | | | | | | | |
| **Adverse event monitoring** | 7.3 | 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] Immediately after the last surgical suture

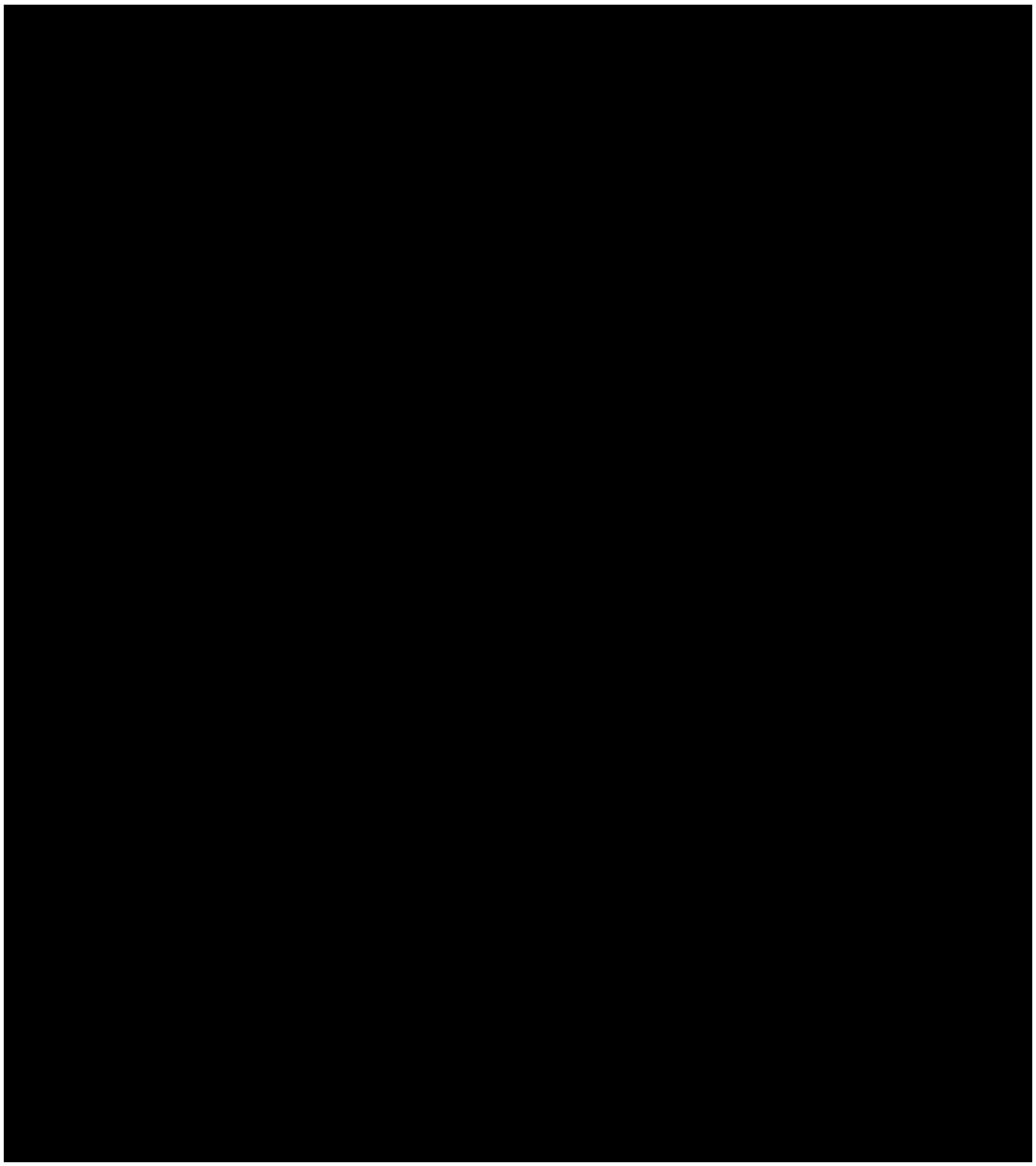
[2] For major surgeries, mandatory for the first 3 postoperative doses

[3] 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.

S, performed by surgeon; H, performed by hematologist; I performed by Investigator

# PROTOCOL SIGNATURES

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and applicable regulatory requirements.



# PROTOCOL SIGNATURES

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and applicable regulatory requirements.

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# LIST OF ABBREVIATIONS

| Abbreviation | Description |
|---|---|
| ABR | Annualized Bleeding Rate |
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| ALAT | Alanine Aminotransferase |
| ANOVA | Analysis of Variance |
| ASAT | Aspartate Transaminase |
| AUC | Area Under the Concentration-Time Curve |
| $AUC_{norm}$ | AUC Normalized for the Administered Dose |
| BE | Bleeding Episode |
| BU | Bethesda Units |
| BW | Body Weight |
| CHR | Chromogenic (Assay) |
| CI | Confidence Interval |
| CL | Clearance |
| $C_{max}$ | Maximum Plasma Concentration |
| eCRF | Electronic Case Report Form |
| ED | Exposure Day |
| EDC | Electronic Data Capture |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HBV | Hepatitis B Virus |
| HCV | Hepatitis C Virus |
| HIV | Human Immunodeficiency Virus |
| IEC | Independent Ethics Committee |
| IMP | Investigational Medicinal Product |
| IRB | Institutional Review Board |
| ITT | Intention-To-Treat |
| IVR | In Vivo Recovery |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRT | Mean Residence Time |
| OS | One-Stage (Assay) |
| PK | Pharmacokinetic |
| PP | Per Protocol |
| PTP | Previously Treated Patient |
| PUP | Previously Untreated Patient |

| | |
|---|---|
| SABR | Spontaneous Annualized Bleeding Rate |
| SAE | Serious Adverse Event |
| SAF | Safety Analysis Set |
| SAP | Statistical Analysis Plan |
| SAR | Suspected Adverse Reaction |
| SC | Subcutaneous |
| SURG | Surgery (Population) |
| $T_{1/2}$ | In Vivo Half-Life |
| TABR | Total Annualized Bleeding Rate |
| TEAE | Treatment-Emergent Adverse Event |
| $T_{max}$ | Time to Reach Maximum Plasma Concentration |
| Vd | Volume of Distribution |
| VWD | Von Willebrand Disease |
| VWF | Von Willebrand Factor |
| VWF:Ac | Von Willebrand Factor Activity |
| VWF:Ag | Von Willebrand Factor Antigen |

# 1 INTRODUCTION

## 1.1 Hemophilia A

Hemophilia A is an inherited sex-linked disorder of blood coagulation in which affected males do not produce functional coagulation factor VIII (FVIII) in sufficient quantities to achieve satisfactory hemostasis. The incidence of congenital hemophilia A is approximately 1 in 10,000 births. Disease severity is classified according to the level of FVIII activity (% of normal) as mild (>5% to <40%), moderate (1% to 5%), or severe (<1%).

The deficiency in FVIII predisposes patients with hemophilia A to recurrent bleeding episodes (BEs) in joints, muscles, or internal organs, either spontaneously or as a result of accidental or surgical trauma. Without adequate treatment, these repeated hemarthroses and hematomas lead to long-term sequelae with severe disability. Less frequent but more severe bleeding sites are the central nervous system, the urinary or gastrointestinal tract, the eyes, and the retroperitoneum.

Patients with hemophilia A are at high risk of developing major and life-threatening BEs after surgical procedures, even after minor interventions such as tooth extraction. Replacement therapy with exogenous FVIII, either plasma-derived or recombinant, successfully adjusts hemostasis in these patients in a temporary manner.

## 1.2 Wilate

*Wilate* is a plasma-derived, stable, highly purified, double virus inactivated concentrate of freeze-dried active von Willebrand factor (VWF) and factor VIII (FVIII) prepared from cryoprecipitate and intended for the treatment of patients with von Willebrand disease (VWD) and/or hemophilia A. By introducing new biotechnological methods and optimized chromatographic media into the *Wilate* manufacturing process, it has been possible to manufacture a preparation containing the FVIII/VWF complex in its native form and almost devoid of lower molecular weight proteins.

Overall, 14 prospective clinical studies with *Wilate* have been completed, 8 in patients with VWD and 6 in patients with hemophilia A. The 6 clinical studies with *Wilate* in patients with hemophilia A were open, non-controlled studies investigating the efficacy and safety of the product in the prevention and treatment of BEs as well as in surgical prophylaxis in a total of 109 individual patients with severe hemophilia A. Of these, 81 were previously treated patients (PTPs) and 28 were previously untreated patients (PUPs).

Five of the 6 studies investigated the efficacy of *Wilate* both in the prevention and treatment of BEs and in surgical prophylaxis, and 1 study assessed the efficacy of *Wilate* in surgical prophylaxis only.

*Wilate* received its first market authorization in Germany in February 2005 and is currently licensed in 65 countries worldwide. In Europe, *Wilate* is approved for the treatment of both VWD and hemophilia A. In the USA, it is approved for the treatment of VWD only.

This study (WIL-30) in children aged 1 to <12 years is performed to obtain approval of *Wilate* for the treatment of hemophilia A in the USA and is carried out alongside a similar study (WIL-27) in patients with severe hemophilia A ≥12 years of age.

A summary of findings from nonclinical and clinical studies with *Wilate* is provided in the product's Investigator's Brochure.

## 1.3 Rationale for Conducting the Study

The purpose of this study is to obtain additional data on the PK profile, safety, and efficacy of *Wilate* in previously treated children with hemophilia A, thus supplementing the existing database to obtain approval of *Wilate* for the indication hemophilia A in the USA.

## 1.4 Dose Rationale

### 1.4.1 Dose for PK Assessment

The dose used for PK assessment, i.e., 50 ± 5 IU/kg, is in line with the current recommendations of the *Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products* (EMA/CHPM/BPWP/144533/2009), which recommends a dose of 25–50 IU/kg. It is expected that this dose will result in measurable FVIII:C plasma concentrations after 48 hours in most, if not all, patients.

The ± 5 IU/kg range (rather than a fixed dose) was included to allow the entire contents of reconstituted vials to be injected rather than taking out an exact volume, which is difficult technically and might result in dosing errors.

### 1.4.2 Doses for Prophylaxis

The doses for prophylaxis (20–40 IU/kg *Wilate*/kg BW given at intervals of 2 to 3 days), the treatment of BEs and perioperative prophylaxis (see **Section 5.4**), are as indicated in the European Summary of Product Characteristics.

Alternative prophylactic regimens at the discretion of the Investigator are also acceptable.

## 1.5 Benefit-Risk Statement

The following adverse reactions are known to occur with other VWF/FVIII preparations and may also occur with the use of *Wilate*:

- **Hypersensitivity or allergic reactions** (which may include angioedema, burning, and stinging at the infusion site, chills, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed upon use of *Wilate* and may, in some cases, progress to severe anaphylaxis (including shock) with or without fever. In rare occasions, fever has been observed.
- The **formation of neutralizing antibodies (inhibitors) to FVIII** is a known complication in the management of hemophilia A. These inhibitors are usually IgG immunoglobulins directed against the FVIII procoagulant activity, which are quantified in Bethesda Units (BU) per mL of plasma. As preventive measure, hemophilia A patients should not be switched thoughtlessly from one FVIII concentrate to another. Patients should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests.
- As for all medicinal products prepared from human blood or plasma, infectious diseases due to transmission of infective agents cannot be totally excluded. This applies also to pathogens of hitherto unknown origin. The manufacturing process of *Wilate*, which includes 2 viral inactivation steps with different chemical/physical action principles represents a high standard for plasma-derived concentrates in terms of pathogen safety. The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and for the non-enveloped hepatitis A virus. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19.

In view of its state-of-the-art manufacturing process and available clinical and postmarketing evidence, the benefit-risk evaluation of *Wilate* is positive.

# 2 STUDY OBJECTIVES

## 2.1 Primary Objective

The primary objective of this study is to determine the **FVIII:C pharmacokinetics (PK) for *Wilate*** in previously treated patients (PTP) with severe hemophilia A aged 1 to <12 years.

## 2.2 Secondary Objectives

The secondary objectives of this study are to:

- Determine the **efficacy of *Wilate* in prophylactic treatment**
- Determine the **efficacy of *Wilate* in the treatment of breakthrough bleeding episodes (BEs)**
- 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**.

# 3 INVESTIGATIONAL PLAN

## 3.1 Study Endpoints

### 3.1.1 Primary Endpoint

The primary endpoint of this study is the PK profile of *Wilate*.

The PK profile is based on the following baseline PK parameters for FVIII:C using both the chromogenic (CHR) and one-stage (OS) assays and actual IMP potencies:

- Area under the curve (AUC) and AUC normalized for the administered dose ($AUC_{norm}$)
- 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)

### 3.1.2 Secondary Endpoints

The secondary endpoints of this study are the:

1. Total annualized bleeding rate (TABR)

   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.
2. Spontaneous annualized bleeding rate (SABR), calculated in analogy with TABR
3. Efficacy of *Wilate* in the treatment of breakthrough BEs based on the proportion of BEs successfully treated with *Wilate*
4. *Wilate* consumption data (FVIII IU/kg per week per patient) for prophylaxis
5. Incremental IVR of *Wilate* over time (at baseline, and at 3 and 6 months of treatment)
6. Association between AB0 blood type and the FVIII:C half-life of *Wilate*
7. Association between VWF:Ag concentration and the FVIII:C half-life of *Wilate*
8. Safety and tolerability of *Wilate* by monitoring adverse events (AEs) throughout the study
9. Immunogenicity of *Wilate* by testing for FVIII inhibitors
10. Virus safety in terms of parvovirus B19

### 3.1.3 Exploratory Endpoint

An exploratory endpoint of this study is the descriptive efficacy of *Wilate* in surgical prophylaxis.

## 3.2 Overall Study Design and Plan

This is a prospective, non-controlled, international, multi-center phase 3 study investigating the FVIII:C pharmacokinetics, efficacy, safety, and immunogenicity of *Wilate* in previously treated children with severe hemophilia A aged 1 to <12 years.

Overall, 10 PTPs (5 patients aged 1 to <6 years of age and 5 patients aged 6 to <12 years) will be enrolled into this study by approximately 5 study sites in Europe. The aim is to obtain data on 8 patients (4 patients per age group) who are evaluable for the primary endpoint, i.e., the PK profile of *Wilate*. Enrolled patients will be replaced only if they do not complete the PK assessment.

At baseline, all patients will undergo a 2-day PK Assessment Phase of 1 dose of 50 IU ± 5 IU *Wilate*/kg BW. The study is scheduled to start in the 4th quarter of 2017 and to be completed in the 3rd quarter of 2018. The planned duration for an individual patient is at least 6 months (+2 weeks) and at least 50 EDs, plus a Follow-up Contact 30 (±3) days after the Completion Visit.

The primary objective of this study is to determine the FVIII:C pharmacokinetics for *Wilate*. Secondary objectives of this study include the total and spontaneous annualized bleeding rates, the efficacy of *Wilate* in the treatment of breakthrough BEs as well as the product's safety and tolerability. An additional objective is the descriptive efficacy of *Wilate* in surgical prophylaxis.

## 3.3 Discussion of Study Design

This prospective, non-controlled, international, multi-center phase 3 study was designed keeping in mind the FDA Draft 'Guidance for Industry on the General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products.' For the choice of the sample size we used the feedback provided by FDA with regard to the number of patients needed in a different paediatric age group in the WIL-27 study (IND 17181, FDA advice / information request dated 13-Dec-2016).

Because clearance of FVIII differs between adolescents and children, this study in children aged 1 to <12 years is performed to complement PK data on *Wilate* in adolescents and adults.

During the study, safety and efficacy data will also be collected.

# 4 STUDY POPULATION

## 4.1 Population Base

### 4.1.1 Number of Patients

Overall, 10 PTPs (5 patients aged 1 to <6 years of age and 5 patients aged 6 to <12 years) will be enrolled into this study.

The aim is to obtain evaluable data on 8 patients who complete both the 2-day PK Phase and the 6-month Prophylactic Treatment Phase. Of the 8 evaluable patients, 4 patients must be 1 to <6 years of age, and another 4 patients must be 6 to <12 years of age. Enrolled patients will be replaced only if they do not complete the PK assessment.

### 4.1.2 Inclusion Criteria

Patients who meet all of the following criteria are eligible for the study:

1. Severe hemophilia A (<1% FVIII:C) according to medical history
2. Male patients aged 1 to <12 years
3. Previous treatment with a FVIII concentrate for at least 50 exposure days (EDs)
4. Immunocompetence (CD4+ count >200/µL)
5. Voluntarily given, fully informed written and signed consent obtained by the patient's parent(s) or legal guardian and, depending on the children's developmental stage and intellectual capacity, informed assent by the patients before any study-related procedures are performed

The interval between the Screening Visit and the PK Visit **should not exceed 30 days**. If the 30-day interval is exceeded, determination of the CD4+ count is to be repeated and must be >200/µL for patients to be enrolled (i.e., inclusion criterion no. 4).

### 4.1.3 Exclusion Criteria

Patients who meet any of the following criteria are *not* eligible for the study:

1. Any coagulation disorders other than hemophilia A
2. History of FVIII inhibitor activity (≥0.6 BU) or detectable FVIII inhibitory antibodies (≥0.6 BU using the Nijmegen modification of the Bethesda assay) at screening, as determined by the central laboratory
3. Severe liver or kidney diseases (alanine aminotransferase [ALAT] and aspartate transaminase [ASAT] levels >5 times of upper limit of normal, creatinine >120 µmol/L)
4. Patients receiving or scheduled to receive immunomodulating drugs (other than antiretroviral chemotherapy), such as alpha-interferon, prednisone (equivalent to >10 mg/day), or similar drugs

5. Treatment with any investigational medicinal product in another interventional clinical study currently or within 4 weeks before enrollment
6. Hemoglobin level < 9 g/dL at the Screening Visit

## 4.2 Prior and Concomitant Therapy

Patients receiving or scheduled to receive immunomodulating drugs (other than anti-retroviral chemotherapy), such as alpha-interferon, prednisone (equivalent to >10 mg/day), or similar drugs may not be enrolled.

Concomitant therapies not interfering with the objectives of the study are permitted. Details of any concomitant medications must be recorded in the electronic Case Report Form (eCRF).

## 4.3 Withdrawal and Replacement of Patients

### 4.3.1 Premature Patient Withdrawal

Patients have the right to withdraw from the study at any time for any reason, without the need to justify their decision. The Investigator also has the right to withdraw patients in case of AEs, poor compliance, or other reasons.

For any withdrawals after study entry, the Investigator will obtain all the required details and document the reason(s) for discontinuation. If the reason for withdrawal of a patient is an AE, the main specific event or laboratory test will be recorded, and the Investigator will make thorough efforts to clearly document the outcome.

### 4.3.2 Patient Replacement Policy

Enrolled patients will be replaced only if they do not complete the PK assessment.

### 4.3.3 Assignment of Patients to Treatment

The Investigator will enter a unique identifier for each patient in both the eCRF and the confidential patient identification list and inform the monitor of any new patient enrolled.

Patients who enroll in the study will not be permitted to re-enroll.

## 4.4 Relevant Protocol Deviations

In case of any major protocol deviation, the Investigator and Octapharma will decide on the further participation of the patient in this study after having discussed all relevant aspects.

# 5 INVESTIGATIONAL MEDICINAL PRODUCT

## *5.1* Characterization of *Wilate*

*Wilate*, produced from the plasma of human donors, is presented as a powder and solvent for intravenous injection containing nominally 500 IU/1000 IU human von Willebrand factor (VWF) and human FVIII per vial. The ratio between von Willebrand factor ristocetin cofactor activity (VWF:RCo) and FVIII:C is 1:1.

The product contains approximately 100 IU/mL human coagulation factor VIII when reconstituted with 5 mL/10 mL water for injections with 0.1% Polysorbate 80. The FVIII potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The injection or infusion rate should be 2–3 mL per minute.

## 5.2 Packaging and Labelling

Final labelling will comply with the national requirements of each country where the study is conducted.

## 5.3 Conditions for Storage and Use

The powder and solvent vials must be stored in a refrigerator (2–8°C). The vials must be kept in the outer carton to protect from light and must not be frozen.

The product can be stored at room temperature (max. 25°C) for 2 months. In this case, the shelf-life expires 2 months after the product has been taken out of the refrigerator for the first time.

The Investigator and any authorized personnel at the site will ensure that the IMP is stored in appropriate conditions with restricted access and in compliance with national regulations.

## 5.4 Dose and Dosing Schedule

### 5.4.1 PK Assessment Phase

In the 2-day PK Assessment Phase performed before the start of the Prophylactic Treatment Phase, *Wilate* will be administered to all patients as a single dose of 50 ± 5 IU kg BW.

### 5.4.2 Prophylactic Treatment Phase

In the Prophylactic Treatment Phase, *Wilate* should be administered every 2 to 3 days at a dose of 20–40 IU/kg BW for 6 months (+2 weeks) and at least 50 EDs.

Alternative prophylactic regimens at the discretion of the Investigator are also acceptable.

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

### 5.4.3 Treatment of Breakthrough BEs

The dose (and duration) of treatment of BEs will depend on the location and extent of bleeding and on the clinical condition of the patient. The dose calculation is based on the empirical finding that 1 IU FVIII:C/kg BW raises the plasma level by 1.5–2.0% of normal activity. The recommended dose is determined using the following formula:

*Recommended units = body weight (kg) x desired factor VIII rise (%) (IU/dL) x 0.5*

In the case of the following hemorrhagic events, the factor VIII activity should not fall below the given plasma FVIII activity level (%) in the corresponding period. The following can be used to guide dosing in BEs:

- **Early hemarthrosis, muscle bleeding, or oral bleeding**
  Target FVIII level: 20–40%
  Recommended dose: 10–20 IU/kg
  Repeat injection every 12–24 hours. At least 1 day, until the BE as indicated by pain has resolved or healing has been achieved.
- **More extensive hemarthrosis, muscle bleeding, or hematoma**
  Target FVIII level: 30–60%
  Recommended dose: 15–30 IU/kg
  Repeat injection every 12–24 hours for 3 to 4 days or more until pain and disability have resolved.
- **Life-threatening hemorrhages**
  Target FVIII level: 60–100%
  Recommended dose: 30–50 IU/kg
  Repeat injection every 8–24 hours until threat has resolved.

### 5.4.4 Surgical Prophylaxis

- **Minor surgeries, including tooth extractions**
  Target FVIII level: 30–60%
  Recommended dose: 15–30 IU/kg
  Every 24 hours, at least 1 day, until healing is achieved.
- **Major surgeries**
  Target FVIII level: 80–100% (pre- and postoperative)
  Recommended dose: 40–50 IU/kg
  Repeat injection every 8–24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a FVIII activity of 30% to 60%.

During treatment, appropriate determination of FVIII:C levels is advised to guide the dose to be administered and the frequency of repeated infusions. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (FVIII:C) is indispensable. Individual patients may vary in their response to FVIII treatment, achieving different half-lives and recoveries.

## 5.5 Preparation and Method of Administration

For more information on the method of administration of *Wilate*, please see the European Summary of Product Characteristics.

Throughout the study, several batches of *Wilate* will be used, and these will be recorded in the clinical study report.

## 5.6 Blinding, Emergency Envelopes, and Breaking the Study Blind

Not applicable.

## 5.7 Treatment Compliance

### 5.7.1 Drug Dispensing and Accountability

Any IMP provided to the site will be accounted for. This includes IMP received at the site, IMP dispensed to patients, and IMP returned unused by the patient.

A Drug Inventory and Dispensing Log will be kept current by the Investigator, detailing the dates and quantities of IMP received and dispensed to each patient and the remaining quantity. The inventory and dispensing log will be available to the monitor to verify drug accountability during the study.

Unused IMP can be destroyed at the study site or returned to the Sponsor for destruction. Destruction can be initiated only after accountability has been verified and fully reconciled by the monitor and after the Sponsor has granted written approval of destruction.

### 5.7.2 Assessment of Treatment Compliance

For PK and IVR assessments at baseline and at 3 and 6 months, the IMP will be administered at the study site, with compliance under the control of the Investigator.

In the Prophylactic Treatment Phase, compliance will be assessed on the basis of the completed patient diaries and returned vials of *Wilate*.

# 6 STUDY CONDUCT

The flow chart of assessments for PK assessment and prophylactic treatment by study visit is given on **page 14**. The flow chart for surgical assessments is given on page **16**. Details on the individual assessments and methods are provided in **Section 7**.

## 6.1 Observations by Visit for PK Assessment and Prophylactic Treatment

All enrolled patients will participate in the following study visits:

- Screening Visit
- PK Visit
- Day-14 Visit
- Day-30 Visit
- 3-Month Visit
- Completion Visit
- Follow-up Contact 30 days after Completion Visit

### 6.1.1 Screening Visit

The following assessments will be performed during the Screening Visit:

- Obtaining voluntarily given, written (signed and dated) informed consent
- Inclusion and exclusion criteria
- Demographic characteristics
- Weight
- Height
- Medical history (including FVIII treatment during the last 6 months before screening)
- Vital signs
- Physical examination
- Hemophilia Joint Health Score (HJHS), unless obtained within 3 months before the Screening Visit
- Blood sampling for the following purposes:
  - Routine safety laboratory
  - Determination of CD4+ levels
  - Determination of AB0 blood group (unless derived from medical history)
  - Determination of FVIII inhibitors
  - Testing for parvovirus B19 antibodies
  - Retention sample for possible additional virus marker testing
- Concomitant medications

The interval between the Screening Visit and the PK Visit **should not exceed 30 days.** If the 30-day interval is exceeded, determination of the CD4+ count is to be repeated and must be >200/µL for patients to be enrolled (i.e., inclusion criterion no. 4, see **Section 4.1.2**).

Any BEs occurring between the Screening Visit and the PK Visit should be treated with the patient's previously used FVIII concentrate. Similarly, prophylactic treatment between the Screening Visit and the PK Visit should be done with the patient's previously used FVIII concentrate.

### 6.1.2 PK Visit

Patients will receive *Wilate* at a dose of 50 ± 5 IU/kg (labelled dose) after a washout period of at least 72 hours from their last FVIII injection. Patients must not be experiencing any bleeding.

The following assessments will be performed:

- **Body weight** before injection
- Blood samples will be taken for the following purposes and at the following time points:
  - **FVIII:C plasma concentration (OS and CHR) for PK assessment** within 1 h before injection and 15±5 min, 1 h (±5 min), 6 h (±30 min), 24±2 h, and 48±2 h after the end of injection
  - **Safety laboratory** before and 48±2 h after injection
  - **FVIII inhibitor** before injection
  - Plasma **VWF:Ag** and **VWF:Ac** within 1 h before injection and 15±5 min after the end of injection
- **Vital signs** before injection as well as 1 h (±5 min) and 48±2 h after injection
- **AE monitoring**
- **Concomitant medications**

At the end of this visit, patients will **receive a patient diary**. The Investigator will explain to the patient how to fill in the diary and emphasize the importance of carefully documenting all treatment details, AEs, and concomitant medications. Also, patients will be **provided with IMP** for home treatment. They will be re-supplied whenever necessary during the study.

**The first prophylactic injection of *Wilate* after the PK Visit marks the beginning of the Prophylactic Treatment Phase.**

### 6.1.3 Day-14 Visit

The Day-14 Visit will take place 14–21 days after the start of the Prophylactic Treatment Phase, if possible after a washout period of at least 48 hours from the patient's latest FVIII injection. The following assessments will be performed:

- **Review of patient diary**
- Blood samples will be taken for the following purposes and at the following time points:
  - **FVIII inhibitor** before injection
  - Plasma **VWF:Ag** and **VWF:Ac** before injection
- **AE monitoring**
- **Concomitant medication**

### 6.1.4 Day-30 Visit

The Day-30 Visit will take place 30±3 days after the start of the Prophylactic Treatment Phase, if possible after a washout period of at least 48 hours from the patient's latest FVIII injection. The following assessments will be performed:

- **Same assessments as for Day-14 Visit**

### 6.1.5 3-Month Visit

The 3-Month Visit will take place 3 months (±2 weeks) after the start of the Prophylactic Treatment Phase.

A prophylactic injection of *Wilate* will be administered, if possible after a washout period of at least 48 hours from the patient's latest FVIII injection. Patients must not be experiencing any bleeding.

The following assessments will be performed:

- **Review of patient diary**
- **Body weight** before injection
- Blood samples will be taken for the following purposes and at the following time points:
  - **FVIII:C plasma concentration (OS and CHR) for IVR assessment** within 1 h before injection of the prophylactic dose and 15±5 min after the end of the injection
  - **Safety laboratory** before injection
  - **FVIII inhibitor** before injection
  - Plasma **VWF:Ag** and **VWF:Ac** within 1 h before injection and 15±5 min after the end of injection
- **Vital signs** before and 15±5 min after the end of injection
- **AE monitoring**
- **Concomitant medication**

### 6.1.6 Study Completion (6-Month) Visit

The Study Completion Visit will take place 6 months (+2 weeks) after the start of the Prophylactic Treatment Phase.

A prophylactic injection of *Wilate* will be administered, if possible after a washout period of at least 48 hours from the patient's latest FVIII injection. Patients must not be experiencing any bleeding.

The following assessments will be performed:

- **Review of patient diary**
- **Body weight** before injection
- Blood samples will be taken for the following purposes and at the following time points:
  - **FVIII:C plasma concentration (OS and CHR) for IVR assessment** within 1 h before injection of the last prophylactic dose and 15±5 min after the end of the injection
  - **Safety laboratory** before and 15±5 minutes after injection
  - **FVIII inhibitor** before injection
  - Plasma **VWF:Ag** and **VWF:Ac** within 1 h before injection and 15±5 min after the end of injection
  - **Parvovirus B19 antibodies** before injection, if first sample was negative
- **Vital signs** before and 15±5 min after the end of injection
- **AE monitoring**
- **Concomitant medication**
- **Physical examination**

All used and unused IMP vials will be returned by the patient.

Patients prematurely withdrawing from the study for any reason will also be invited to attend the Study Completion Visit.

### 6.1.7 Follow-up Contact 30 days after Study Completion Visit

The purpose of the Follow-up Contact 30 (±3) days after the 6-month Study Completion Visit is to **document any thromboembolic events**, whether or not they are suspected to be related to study treatment.

The Follow-up Contact may take either the form of a personal visit by the patient to the study site or a telephone call by the Investigator. Any relevant AEs are to be recorded on the AE page of the eCRF.

### 6.1.8 Unscheduled Visits and Additional Measures

If inhibitor development is suspected (e.g., based on an unexplained need to increase the dose, lack of efficacy of IMP injections, or prolonged bleeding), FVIII inhibitor tests in addition to those scheduled during study visits will be performed and documented (see **Section 7.3.5.1**).

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. If inhibitor development is confirmed by the second sample analyzed in the central laboratory, patients with low-titer inhibitors (<5 BU) may continue treatment with *Wilate*, while patients with high-titer inhibitors will be discontinued from the study.

Other reasons for unscheduled visits may be the occurrence of serious AEs or hospitalizations because of severe BEs or because of a surgical intervention.

### 6.1.9 Surgical Visits

Patients may undergo surgical interventions in the course of the study. Whether or not patients will be hospitalized will depend on the type and severity of the surgery and be at the discretion of the Investigator.In patients undergoing major surgeries, standard methods of postsurgical thromboprophylaxis, such as gradated compression stockings and early mobilization, should be used to prevent venous thromboembolism.

For the flow chart of assessments for surgeries, see **page 16**. For details on the surgery data to be documented and the surgical efficacy assessments to be performed, see **Section 7.2.5** and **Section 7.2.6**.

## 6.2 Duration of Study

### 6.2.1 Planned Duration for an Individual Patient

The planned duration of treatment for an individual patient is about 6 months (+2 weeks) and at least 50 EDs, plus a Follow-up Contact 30 (±3) days after the Completion Visit.

### 6.2.2 Planned Duration for the Study as a Whole

The study will be considered completed at the time of database lock.

The estimated start of the study (enrollment of first patient) is the 4th quarter of 2017, and the estimated end of the study (database lock) is the 3rd quarter of 2018.

### 6.2.3 Premature Termination of the Study

Both the Investigator and the Sponsor reserve the right to terminate the study at any time. In this event, any necessary procedures will be arranged on an individual study basis after review and consultation by both parties. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the subjects'/patients' interests.

Regulatory authorities and IECs/IRBs should be informed in accordance with national regulations. Early termination of the study as a whole or by center may apply for the following reasons:

#### *6.2.3.1 Early Termination of the Entire Clinical Study*

At any time, the study as a whole will be terminated prematurely if new toxicological or pharmacological findings or safety reports invalidate the earlier positive benefit-risk-assessment.

#### *6.2.3.2 Early Termination at an Individual Study Center*

At any time, the study can be terminated at an individual center if:

- The center cannot comply with the requirements of the protocol.
- The center cannot comply with GCP standards.
- The required recruitment rate is not met.

Should the study be prematurely terminated, all study materials (completed and partially completed CRFs, IMPs, etc.) must be returned to the Sponsor.

# 7 ASSESSMENTS AND METHODS

## 7.1 Demographic and Baseline Information

The following information will be recorded during the Screening Visit (see **Section 6.1.1**):

### 7.1.1 Demographic and Baseline Characteristics

The demographic and baseline characteristics are age, ethnic origin, height, weight, CD4+ levels, and AB0 blood group (may also be derived from the patient's medical history). In addition, the Hemophilia Joint Health Score (HJHS) will be obtained (unless done within 3 months before the Screening Visit).

### 7.1.2 Medical History and Concomitant Medications

The medical history will be obtained by interviewing the patient's parents or guardians. Records of past diseases and treatments (e.g., hospital discharge letters) will be obtained for the study files, if available.

Concomitant medications will be also obtained by interview, and information about FVIII dosing in the previous 6 months will be collected.

The history or presence of FVIII inhibitor activity is an exclusion criterion (see **Section 4.1.3**).

## 7.2 Efficacy Assessments

This section summarizes the assessments to be performed for the calculation of the primary (see **Section 3.1.1)** and secondary endpoints (see **Section 3.1.2)** of this study.

### 7.2.1 Pharmacokinetic Evaluation

The following PK parameters for FVIII:C will be determined using a non-compartment model:

- $AUC_{norm}$ and AUC
- 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)

For details on the laboratory analyses, see **Section 7.3.5**.

### 7.2.2 IMP Administration Data

The following parameters will be documented:

- Dates and times of IMP injections
- Doses of IMP in IU and IMP batch numbers
- Purpose of IMP injection (PK, IVR, prophylaxis, treatment of BE, surgery)

### 7.2.3 Bleeding Episode (BE) Data

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

- BE type (spontaneous, traumatic, postoperative, other)
- BE site
- BE severity (minor, moderate, major, life-threatening) (see **Table 1**)
- Date and time the BE first occurred or was first noticed
- Date and time the BE ended
- IMP administration data (see **Section 7.2.2**)
- Assessment of the efficacy of treatment at the end of the BE (see **Section 7.2.4**)

If the treatment of a BE in one bleeding site is interrupted for more than 48 hours, two separate BEs will have to be recorded; if, in addition to the original bleeding site, another bleeding site is affected, these events will be recorded as separate BEs at any time.

All of these parameters will be documented by the patient (together with the Investigator in case of on-site treatments) in the patient diary. Patients who experience a major or life-threatening BE should be treated at the study site, if possible.

Based on these data, the frequency of BEs and the ABR under prophylactic treatment will be calculated.

**Table 1 Categorization for the Severity of Bleeding Episodes**

| Severity | Definition | Example |
|---|---|---|
| **Minor** | Bleeding with few symptoms | Early onset muscle and joint bleeds with no visible symptoms, such as little or no change in the range of motion of affected joint (if joint bleeding event); mild restriction of mobility and activity, scrapes, superficial cuts, bruises, superficial mouth bleeds, and most nose bleeds |
| **Moderate** | Bleeding that involves swelling or pain, including some decrease in range of motion of affected joint (if joint bleeding event) or moderate decrease in mobility and activity | Advanced soft tissue and muscle bleeds into the limbs, bleeding into the joint space, such as the elbow, knee, ankle, wrist, shoulder, hip, foot, or finger |
| **Major** | Bleeding that causes significant pain, substantial decrease in range of motion of affected joint (if joint bleeding event), and incapacity | Complicated joint bleeds, bleeds of the pelvic muscles, eyes |
| **Life-threatening** | | Bleedings in the abdomen, digestive system or chest, central nervous system bleeds, bleedings in the area of the neck or throat or pharynx, or other major trauma |

### 7.2.4 Efficacy of the Treatment of Breakthrough BEs

At the end of a BE, treatment efficacy will be assessed by the patient (together with the Investigator in case of on-site treatment) using the predefined criteria detailed in **Table 2**.

**Table 2 Efficacy Assessment of the Treatment of Breakthrough BEs**

| | |
|---|---|
| **Excellent** | Abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single injection |
| **Good** | Definite pain relief and/or improvement in signs of bleeding within approximately 8–12 hours after an injection, requiring up to 2 injections for complete resolution |
| **Moderate** | Probable or slight beneficial effect within approximately 12 hours after the first injection, requiring more than 2 injections for complete resolution |
| **None** | No improvement within 12 hours, or worsening of symptoms, requiring more than 2 injections for complete resolution |

The **proportion of BEs successfully treated with IMP** will be evaluated for all BEs taken together and by BE severity. All efficacy ratings assessed as either ‘excellent’ or ‘good’ will be considered ‘successfully treated.’

### 7.2.5 Surgical Prophylaxis Data

The following surgery-related parameters will be documented:

- Body weight within 12 hours before the start of surgery
- Safety laboratory tests (hematology, chemistry) within 12 hours before the start of surgery and 24 hours after the end of surgery (see **Section 7.3.5.2**)
- Vital signs within 12 hours before the start of surgery (before blood sampling)
- Type of surgery (planned or emergency)
- Location of surgery
- Severity of surgery (minor, major) (see definitions under **(a)** below)
- Expected duration of surgery
- Actual duration of surgery (start and end times, i.e., skin to skin)
- Details on IMP dose(s) given pre-, intra-, or postoperatively (see **Section 7.2.2**)
- Pre-, intra-, and postoperative FVIII plasma levels (see definitions under **(b)** below)
- Expected and actual blood loss (see item **(d)** below)
- Presence of wound hematomas and whether or not they require surgical evacuation
- Efficacy assessments at the end of surgery by surgeon (see **Section 7.2.6.1**)
- Efficacy assessment at the end of the postoperative period by hematologist (see **Section 7.2.6.2**)
- Overall efficacy assessment by the Investigator (see **Section 7.2.6.3**)
- Narrative describing the outcome and efficacy of the intervention
- Monitoring of AEs
- Details on concomitantly administered products, including any blood or blood product transfusions but excluding drugs given for routine anesthesia
- Inhibitor testing (see **Section 7.3.5.2**), with a plasma sample obtained within 3–8 weeks after the end of the surgery; this visit can coincide with another study visit with scheduled inhibitor testing.

***(a) Severity of surgery***

Surgeries are defined as **major** if any of the following criteria are met:

- General or spinal anesthesia required
- Opening into the great body cavities required
- Hemostatic therapy for at least 6 days required
- Orthopedic 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

The classification is made prospectively. All other surgeries are classified as **minor**.

***(b) Definitions of periods and time points before, during, and after surgery***

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

***(c) FVIII plasma levels***

FVIII plasma levels will be documented for the following time points:

- Immediately (≤ 30 min) before and 30±15 min after preoperative injection of IMP
- Immediately (≤ 30 min) before and 30±15 min after each intraoperative bolus dose, if any
- Immediately (≤ 30 min) before and 30±15 min after each postoperative dose, if any; in case of major surgery, the determination of FVIII plasma levels is mandatory for the first 3 postoperative doses

***(d) Estimated and actual blood loss***

Before surgery, the surgeon will provide written estimates of both the **average** and **maximum volume (mL) of expected blood loss** for the planned surgical procedure for a patient with normal hemostasis of the same sex, age, and stature as the patient enrolled in this study. After surgery, the surgeon will estimate the **actual blood loss** experienced by the patient.

### 7.2.6 Efficacy in Surgical Prophylaxis

Efficacy will be assessed at the end of surgery by the surgeon (see **Section 7.2.6.1**) and at end of the postoperative period by the hematologist (see **Section 7.2.6.2**). In both cases, predefined assessment criteria will be used.

In addition, there will be an overall assessment of efficacy (see **Section 7.2.6.3**).

#### *7.2.6.1 At the End of Surgery (by Surgeon)*

At the end of surgery, the hemostatic efficacy of *Wilate* will be assessed by the surgeon using the criteria listed in **Table 3**.

**Table 3 Efficacy Assessment at the End of Surgery**

| | |
|---|---|
| **Excellent** | Intraoperative blood loss was lower than or equal to the average expected blood loss for the type of procedure performed in a patient with normal hemostasis and of the same sex, age, and stature. |
| **Good** | Intraoperative blood loss was higher than the average expected blood loss but lower or equal to the maximal expected blood loss for the type of procedure in a patient with normal hemostasis. |
| **Moderate** | Intraoperative blood loss was higher than the maximum expected blood loss for the type of procedure performed in a patient with normal hemostasis, but hemostasis was controlled. |
| **None** | Hemostasis was uncontrolled, necessitating a change in the clotting factor replacement regimen. |

#### *7.2.6.2 At the End of the Postoperative Period (by Hematologist)*

At the end of the postoperative period, the hemostatic efficacy of *Wilate* will be assessed by the hematologist using the criteria listed in **Table 4**.

**Table 4 Efficacy Assessment at the End of the Postoperative Period**

| | |
|---|---|
| **Excellent** | No postoperative bleeding or oozing that was not due to complications of surgery. All postoperative bleeding (due to complications of surgery) was controlled with *Wilate* as anticipated for the type of procedure. |
| **Good** | No postoperative bleeding or oozing that was not due to complications of surgery. Control of postoperative bleeding due to complications of surgery required increased dosing with *Wilate* or additional injections not originally anticipated for the type of procedure. |
| **Moderate** | Some postoperative bleeding and oozing that was not due to complications of surgery. Control of postoperative bleeding required increased dosing with *Wilate* or additional injections not originally anticipated for the type of procedure. |
| **None** | Extensive uncontrolled postoperative bleeding and oozing. Control of postoperative bleeding required use of an alternate FVIII concentrate. |

#### *7.2.6.3 Overall Efficacy Assessment at the End of the Postoperative Period (by Investigator)*

Overall efficacy using the 'excellent,' 'good,' moderate,' and 'none' scale taking both the intra- and postoperative assessments into account will be assessed by the Investigator.

**Table 5 Algorithm for the Overall Efficacy Assessment for Surgical Prophylaxis**

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

## 7.3 Safety Assessments

### 7.3.1 Assessments for Safety Endpoints

Any of the following drug safety information shall be collected:

- Adverse events (AEs) and serious adverse events (SAEs) temporally associated with the administration of IMP (for definitions and reporting requirements, see **Sections 7.3.2**, **7.3.3**, and **7.3.4**)
- Drug overdose, interaction, medication error, and post-study SAEs (see **Section 7.3.7**)

### 7.3.2 Adverse Events (AEs)

#### *7.3.2.1 Definitions*

- **Adverse event (AE):** An AE is any untoward medical occurrence in a study subject/patient receiving an IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.
- **Treatment-emergent adverse event (TEAE):** A TEAE is an AE that started or worsened after the start of IMP infusion.

- **Adverse drug reaction (ADR):** An ADR is any noxious and unintended response to an IMP related to any dose. The phrase 'response to an IMP' means that a causal relationship between the IMP and an AE carries at least a reasonable possibility, i.e., the relationship cannot be ruled out.
- **Other significant AEs:** Any marked laboratory abnormalities or any AEs that lead to an intervention, including withdrawal of drug treatment, dose reduction, or significant additional concomitant therapy.
- **Withdrawal due to AE/ADR:** AE/ADR leading to discontinuation of treatment with IMP. Any such events will be followed up by the Investigator until the event is resolved or until the medical condition of the subject/patient is stable. All follow-up information collected will be made available to the Sponsor.

#### *7.3.2.2 Collection of AEs*

The condition of the patient will be monitored throughout the study. At each visit, whether scheduled or unscheduled, AEs will be elicited using a standard nonleading question such as "How have you been since the last visit/during the previous study period?" In addition, the Investigator will check the patient diaries for any documented event.

Any AE or ADR which occurs during the study will be noted in detail on the appropriate pages of the CRF. If the patient reports several signs or symptoms representing a single syndrome or diagnosis, the diagnosis should be recorded in the CRF. The Investigator will grade the severity of all AEs or ADRs (mild, moderate, or severe), the seriousness (non-serious or serious), and the causality as defined in **Sections 7.3.2.3**, **7.3.3**, and **7.3.2.4**. The Sponsor is responsible for assessing the expectedness of each ADR (expected or unexpected) as defined in **Section 7.3.2.5**.

In the event of clinically significant abnormal laboratory findings, the tests will be confirmed and the patient followed up until the laboratory values have returned to normal and/or an adequate explanation for the abnormality has become available.

Diseases, signs and symptoms, and/or laboratory abnormalities already present before the first administration of IMP will not be considered AEs unless an exacerbation in intensity or frequency (worsening) occurs.

The Investigator will provide detailed information about any abnormalities and about the nature of and reasons for any action taken as well as any other observations or comments that may be useful for the interpretation and understanding of an AE or ADR.

#### *7.3.2.3 Severity of AEs*

The severity of AEs will be graded as follows:

- **Mild:** an AE, usually transient, which causes discomfort but does not interfere with the patient's routine activities
- **Moderate:** an AE which is sufficiently discomforting to interfere with the patient's routine activities
- **Severe:** an AE which is incapacitating and prevents the pursuit of the patient's routine activities

The grading of an AE is up to the medical judgment of the Investigator and will be decided on a case-by-case basis.

#### *7.3.2.4 Causality of AEs*

The relationship of AEs to the administered IMP will be assessed by the Investigator:

- **Probable:** reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable. A reaction that follows a reasonable temporal sequence from administration of the IMP; or that follows a known or expected response pattern to the suspected medicine; or that is confirmed by stopping or reducing the dosage of the medicine and that could not reasonably be explained by known characteristics of the subject's/patient's clinical state.
- **Possible:** reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence. A reaction that follows a reasonable temporal sequence from administration of the IMP; that follows a known or expected response pattern to the suspected medicine; but that could readily have been produced by a number of other factors.
- **Unlikely:** reports not following a reasonable temporal sequence from IMP administration. An event which may have been produced by the subject's/patient's clinical state or by environmental factors or other therapies administered.
- **Not related (unrelated):** events for which sufficient information exists to conclude that the etiology is unrelated to the IMP.
- **Unclassified:** reports which for one reason or another are not yet assessable, e.g., because of outstanding information (can only be a temporary assessment).

#### *7.3.2.5 Classification of ADRs by Expectedness*

ADRs will be classified by the Sponsor as either expected or unexpected:

- **Expected:** an ADR that is listed in the current edition of the Investigator's Brochure.
- **Unexpected:** an ADR that is not listed in the current edition of the Investigator's Brochure or that differs because of greater severity or greater specificity.

#### *7.3.2.6 Outcome of AEs*

The outcome of all reported AEs has to be documented as follows:

1. Recovered, resolved
2. Recovering, resolving
3. Not recovered, not resolved
4. Recovered, resolved with sequelae
5. Fatal
6. Unknown

**NOTE:** A patient's **death** per se is not an event, but an outcome. The event which resulted in the patient's death must be fully documented and reported, even in case the death occurs within 4 weeks after IMP treatment end and regardless of whether or not it is considered treatment-related.

#### *7.3.2.7 Action(s) Taken*

AEs requiring action or therapy must be treated with recognized standards of medical care to protect the health and wellbeing of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment in an emergency situation.

The actions taken by the Investigator must be documented:

***(a) General actions taken in the event of an AE***

- None
- Medication (other than IMP) or other (e.g., physical) therapy started
- Test performed
- Other (to be specified)

***(b) IMP-related actions taken in the event of an AE***

- None
- Product withdrawn
- Dose reduced
- Dose increased

The Investigator will follow up on each AE until it has resolved or until the medical condition of the patient has stabilized. Any relevant follow-up information will be reported to the Sponsor.

### 7.3.3 Serious Adverse Events (SAEs)

A **serious AE (SAE)** is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (see below),
- requires hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is another important medical event (see below).

**NOTE:** The term **'life-threatening'** refers to an event in which the subject/patient was, in the view of the reporting Investigator, at immediate risk of death at the time of the event; it does not refer to an event which may hypothetically have caused death had it been more severe.

In deciding whether an AE/ADR is serious, medical judgment should be exercised. Thus, important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed in the definitions above should also be considered serious.

Examples of **'important medical events'** are all suspected transmissions of an infectious agent, which therefore have to be reported as SAE. A suspected virus transmission means that virus antigen has been detected in the patient. A passive transmission of antibodies alone does not constitute a suspected virus transmission. Another such 'important medical event' that has to be reported as an SAE is the development of FVIII inhibitors.

### 7.3.4 AE and SAE Reporting Timelines

All **thromboembolic events**, whether or not they are suspected to be related to study treatment, are to be reported by telephone, fax, or email to the Clinical Trial Manager. They should be documented on AE page in eCRF.

After the Study Completion Visit, all thromboembolic events will continue to be monitored proactively by performing a Follow-up Contact 30 days after the completion visit (see **Section 6.1.7**). They should be documented on AE page in eCRF.

All **SAEs**, whether or not they are suspected to be related to study treatment, are to be reported immediately by telephone, fax, or email to the Clinical Trial Manager.

**CLINICAL TRIAL MANAGER:**

The contact details will also be communicated at the study initiation visit.

In addition, within 24 hours after recognition of an SAE, an Octapharma Serious Adverse Event Report must be completed and submitted to:

**Waivers the from SAE Reporting Requirement**

Waivers from the SAE reporting requirement include surgeries that are elective or were planned before study entry or prolongations of existing hospitalizations for economic or social, but not medical, reasons. Such surgeries or prolongations of hospitalizations should not be considered SAEs.

### 7.3.5 Laboratory Tests

The following laboratory parameters will be determined at the time points specified in the flow charts of assessments on **pages 14** and **16** and in **Section 6**.

#### *7.3.5.1 Central Laboratory*

The following laboratory tests will be done at the central laboratory:

- **FVIII:C** in the vials used for PK injections as well as in plasma using the CHR and OS assays
- **FVIII inhibitor activity** will be determined at each study visit before the injection of *Wilate* using the modified Bethesda assay (Nijmegen modification). Blood sampling for inhibitor testing should preferably be performed at the time of trough FVIII:C levels.

  If inhibitor development is suspected between study visits (e.g., based on an unexplained need to increase the dose, lack of efficacy of IMP injections, or prolonged bleeding) (see also **Section 6.1.8**), additional FVIII inhibitor tests will be performed and documented.

  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. If inhibitor development is confirmed by the second sample analyzed in the central laboratory, patients with low-titer inhibitors (<5 BU) may continue treatment with *Wilate*, while patients with high-titer inhibitors will be discontinued from the study.

- **VWF:Ag** and **VWF:Ac** will be measured at prespecified time points.

  **VWF:Ac** will be measured by INNOVANCE® VWF Ac (Siemens Healthcare Diagnostics), which is a particle enhanced assay for the automated determination of VWF activity in human citrated plasma. The assay principle makes use of the binding of VWF to its receptor Glycoprotein Ib (GPIb). GPIb is the main VWF receptor on platelets. Polystyrene particles are coated with an antibody against GPIb. Recombinant GPIb (two gain-of-function mutations included) is added and binds to the antibody as well as to the VWF of the sample. Due to the gain-of-function mutations, VWF binding to GPIb does not require ristocetin. This VWF binding induces a particle agglutination which can be measured as an increase in extinction by turbidimetric measurements.
- **Virus safety** will be evaluated by taking a plasma sample for parvovirus B19 antibody testing during the Screening Visit. All patients negative during screening will be tested again at the Study Completion Visit.

  A retention serum sample for possible virus marker testing will be taken during the Screening Visit and stored at the central laboratory.

***Central laboratory:***

[redacted]

#### *7.3.5.2 Local Laboratory*

The following laboratory tests will be done by the local laboratories of each study site:

- **Hematology:** red blood cell count, white blood cell count, hemoglobin, hematocrit, and platelet count
- **Chemistry:** total bilirubin, alanine amino transferase, aspartate transaminase, blood urea nitrogen, serum creatinine

**CD4+** and **AB0 blood-type testing** as well as **FVIII:C measurements in case of surgery** will also be done by the local laboratories. Samples for surgery-related FVIII:C testing will also be shipped to the central laboratory for OS and CHR assay assessments.

The methods of determination and normal ranges for each parameter will be provided in the clinical study report.

### 7.3.6 Vital Signs and Physical Examination

The vital signs obtained at the time points specified in **Section 6** are blood pressure, body temperature, heart rate, and respiratory rate.

Physical examinations will be performed at the visits specified in **Section 6**. Both height and weight will be measured at baseline. In addition, weight will be measured at all visits prior to dosing.

### 7.3.7 Other Relevant Safety Information

***(a) Post-study related safety reports***

After the Study Completion Visit, any thromboembolic events will continue to be monitored proactively by performing a Follow-up Contact 30 days after the Study Completion Visit (see **Sections 6.1.7** and **7.3.4**). They should be documented on AE page in eCRF.

In addition, any **SAE** which occurs up to 4 weeks after the last IMP administration should be reported by the Investigator to the Sponsor in case the Investigator becomes aware of it. Proactive monitoring for post-study SAEs is not required.

If any such post-study event is identified, the Investigator will complete an SAE form and transmit it to the Clinical Trial Manager (see **Section 7.3.4**).

Deaths occurring within 4 weeks after the last IMP administration should also be reported, regardless of whether or not they are considered treatment-related.

**Overdose, interaction, medication error**

The following safety relevant information should be reported as AE or, if the reaction fulfils one of the criteria for seriousness, as SAE.

***(b) Drug overdose***

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than the known therapeutic dose that is of clinical relevance. The reaction must be clearly identified as an overdose.

***(c) Drug interaction***

A drug interaction is a situation in which a substance or medicinal product affects the activity of an IMP, i.e., increases or decreases its effects, or produces an effect that none of the products would exhibit on its own. The reaction must be clearly identified as a drug interaction.

***(d) Medication error***

A medication error involves the inadvertent administration or unintended use of a medicinal product which may be caused by the naming, presentation of pharmaceutical form/packaging, or instructions for use/labelling. The reaction must be clearly identified as a medication error.

## 7.4 Appropriateness of Measurements

The criteria for assessing the safety and efficacy of *Wilate* in the prevention and treatment of BEs as well as in surgical prophylaxis are identical to those used in a similar study with *Wilate* in patients aged ≥12 years, i.e., WIL-27. The measurements of the essential tolerability and immunogenicity parameters assessed in this study are also identical to those used in WIL-27. Inhibitor measurements are performed by a central laboratory using validated assays.

# 8 DATA HANDLING AND RECORD KEEPING

## 8.1 Documentation of Data

### 8.1.1 Source Data and Records

Source data are defined as all information related to clinical findings, observations, or other activities in the study, written down in original records or certified copies of original records, allowing reconstruction and evaluation of the clinical study.

The Investigator will maintain adequate source records (e.g., case histories or patient files for each patient enrolled). Source records should be preserved for the maximum period of time required by local regulations.

For each patient enrolled, the Investigator will indicate in the source record(s) that the patient participates in this study.

All data entered in the eCRF must be supported by source data in the patient records.

The Investigator will permit study-related monitoring, audits, IEC/IRB reviews, and regulatory inspections, by providing direct access to the source data/records.

The Investigator may authorize site staff (e.g., sub-investigators, nurses) to enter study data into the eCRF. This must be documented in the Delegation of Authority Log signed by the Investigator.

### 8.1.2 Case Report Forms

For each patient enrolled, an electronic CRF (eCRF) will be completed within the Electronic Data Capture (EDC) system and approved by the Investigator or an authorized sub-investigator.

Study site staff (e.g., research nurse) will be responsible for entering patient data into the validated EDC system. All site personnel will be trained on the EDC system and study-specific eCRFs prior to receiving access to the live database for data entry.

The site is also provided with the approved eCRF Completion Guidelines which will assist in data entry and data issues/questions. The site will be notified once the database is active to begin data entry. Additional site training may be provided as refreshers throughout the study, if needed. All persons allowed to enter or change eCRF data must be listed in the Delegation of Authority Log.

### 8.1.3 Changes to Case Report Form (CRF) Data

Monitors will perform source data verification (SDV) as defined for the study.

If any errors or discrepancies in the eCRFs are found during data entry or review, discrepancies will be generated programmatically within the EDC system, and 'manual' queries will be generated by either a monitor or Data Management.

Discrepancies and queries can only be corrected by the Investigator(s) or other authorized site personnel. An audit trail documents all changes to the data over the entire study period. If the reason for a change is not obvious, a comment must be supplied in the query's response, stating the reason for the change, prior to closing. The study monitor should provide guidance to Investigator(s) and the Investigator(s)' designated representatives on making such corrections.

Once queries have been resolved by the site staff, the resolutions are assessed by Data Management. If the query response provided confirms the data as correct, the discrepancy will be closed. If the response does not adequately address the question raised, a new query will be issued for further clarification.

Manual checks are performed and programs are run throughout the study until the data is clean and the database is ready for lock. All discrepancies will be resolved prior to database lock. There will be a final run of the programmed checks to ensure all discrepancies are closed out, SDV will be confirmed as complete by the monitor, and all eCRFs will be approved by the Investigator prior to database lock.

## 8.2 Information to Investigators

An Investigator's Brochure (IB) will be handed out to the Investigator before the start of the study. The IB contains all information in the Sponsor's possession necessary for the Investigator to be fully and accurately informed about the safety of the IMP under evaluation and the respective benefit-risk ratio.

The IB will be updated by the Sponsor at regular intervals and whenever relevant new information concerning the IMP becomes available.

The Investigator will be informed about the methods for rating relevant study outcomes and for completing eCRFs to reduce discrepancies between participating Investigator and study sites.

The Investigator will be kept informed of important data that relate to the safe use of the IMP as the study proceeds.

## 8.3 Responsibilities

The Principal Investigator is accountable for the conduct of the clinical study. Responsibilities may be delegated to appropriately qualified persons.

A Delegation of Authority Log will be filled in and signed by the Principal Investigator. In accordance with this authority log, study site staff (e.g., sub-investigators, nurses) is authorized to perform tasks relating to the study.

## 8.4 Investigator's Site File

At each study site, the Investigator is responsible for maintaining all records to enable the conduct of the study to be fully documented. Essential documents as required by GCP guidelines and regulations (e.g., copies of the protocol, study approval letters, all original informed consent and assent forms, drug dispensing and accountability logs, correspondence pertaining to the study, etc.) should be filed accurately and kept by the Investigator for the maximum period of time required by local regulations.

The Investigator is responsible for maintaining a confidential patient identification code list, which provides the unique link between named source records and CRF data for the Sponsor. The Investigator must arrange for the retention of this confidential list for the maximum period of time required by local regulations.

No study document should be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified in writing.

## 8.5 Provision of Additional Information

On request, the Investigator will supply the Sponsor with additional data relating to the study, or copies of relevant source records, ensuring that the patient's confidentiality is maintained. This is particularly important when CRFs are illegible or when errors in data transcription are encountered. In case of particular issues or governmental queries, it is also necessary to have access to the complete study records, provided that the patient's confidentiality is protected in accordance with applicable regulations.

# 9 STATISTICAL METHODS AND SAMPLE SIZE

The statistical analysis will be delegated under an agreement of transfer of responsibilities to an external CRO that agrees to meet all Octapharma procedures and policies.

## 9.1 Determination of Sample Size

The sample size of 10 pediatric patients to be enrolled was based on medical and regulatory reasoning. No statistical sample size estimation was performed.

## 9.2 Statistical Analysis

The primary approach to the statistical analysis will be descriptive, presenting sampling statistics (n, mean, standard deviation, quartiles and range) for continuous measurements and absolute and relative frequency counts for categorical/ordinal data. This will be complemented by the presentation of exploratory confidence intervals (CIs) for means or proportions.

A formal Statistical Analysis Plan (SAP) describing all details of the analyses to be performed will be prepared by the study statistician and approved by the Sponsor prior to the start of the statistical analysis.

### 9.2.1 Populations for Analysis

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

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

The **pharmacokinetic (PK) set** will include all patients for whom a valid *Wilate* PK profile has been obtained.

The **per-protocol (PP) set**, i.e., a subset of the FAS, will exclude patients with major protocol deviations which may have an impact on the evaluation of the efficacy outcome parameters. Examples of major and minor protocol deviations will be described in the SAP.

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

A final decision about the classification of protocol deviations and their consequences regarding assignment of patients to analysis sets will be made during the data review meeting. Decisions and outcome will be approved by the Sponsor.

- The analysis of safety will be based on the SAF set.
- Analysis of the PK properties of *Wilate* will be based on the PK set.
- The evaluation of the primary efficacy endpoint will be performed on the FAS (ITT analysis) and on the PP set (PP analysis).
- For secondary endpoints, ITT and additionally PP analyses will be carried out unless these analysis sets are identical.
- Analysis of the efficacy and safety of *Wilate* in surgeries will be based on the SURG set.

### 9.2.2 PK and Efficacy Analysis Plan

*Pharmacokinetic Analysis*

The analysis of the pharmacokinetic profiles of *Wilate* will be based on the FAS and the PP set.

The following PK parameters for FVIII:C will be analysed both for the chromogenic (CHR) and one-stage (OS) assays and actual IMP potencies:

- Area under the curve (AUC) and AUC normalized for the administered dose ($AUC_{norm}$)
- 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)

FVIII:C will be measured in the vials used for PK injections as well as in plasma using the CHR and OS assays.

- AUC of *Wilate* will be calculated from FVIII:C plasma levels measured at predefined time points and normalized for the administered dose ($AUC_{norm}$) using actual IMP potencies.
- All other PK parameters will be calculated from FVIII:C plasma levels measured at predefined time points using actual IMP potencies.
- Incremental IVR will be calculated from FVIII:C plasma levels measured before injection and peak levels obtained in the 15-min post-injection sample using actual IMP potencies.

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.

For all patients, the results of the IVR assessments over time will also be analyzed in summary tables for each time point and their differences to baseline along with 95% CIs for the mean differences.

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*.

*Efficacy of Prophylactic Treatment with Wilate*

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.

The efficacy of prophylactic treatment with *Wilate* will be statistically evaluated by presenting descriptive sampling statistics for the TABR and SABR, along with an exploratory 95% CI for the mean.

*Efficacy in the Treatment of Breakthrough BEs*

To assess the hemostatic efficacy of *Wilate* in the treatment of breakthrough bleedings, a frequency distribution of all such BEs being successfully treated will be presented, along with an exploratory 95% CI.

*Analysis of Other Secondary Endpoints*

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

*Subgroup Analyses*

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

- Age '1 to <6 years'
- Age '6 to <12 years'

### 9.2.3 Safety Analysis Plan

All safety analyses will be based on the SAF population.

The analysis of safety will be based on the occurrence of AEs, the results of the safety laboratory tests, immunogenicity measurements, and the occurrence of parvovirus B19 seroconversions.

AEs will be coded according to the latest Medical Dictionary for Regulatory Activities (MedDRA) version. The analysis will include only treatment-emergent adverse events (TEAEs), i.e., AEs that started or worsened after the start of IMP infusion. All TEAEs, related TEAEs (i.e., TEAEs probably or possibly related to the IMP), and serious TEAEs will be summarized and tabulated according to MedDRA primary system organ class and preferred term.

Patient listings will be provided for patients with SAEs, AEs leading to withdrawal from study, and AEs leading to death.

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.

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

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

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

### 9.2.4 Handling of Missing Data

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

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

## 9.3 Randomization, Stratification, and Code Release

Not applicable.

## 9.4 Interim Analysis

Not applicable.

# 10 ETHICAL/REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

## 10.1 Ethical/Regulatory Framework

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The study protocol and any subsequent amendment(s) will be submitted to an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and to the Regulatory Authority. The study will be conducted in compliance with the protocol, GCP guidelines, and applicable regulatory requirements.

The regulatory application or submission for regulatory approval will be made by the Sponsor or designated third party (e.g., CRO) as required by national law.

## 10.2 Approval of Study Documents

The study protocol, a sample of the patient information and informed consent form, any other materials provided to the patients, and further requested information will be submitted by the Sponsor or the Investigator to the appropriate IEC/IRB and the Regulatory Authority. The study must be approved by the IEC/IRB and the Regulatory Authority before any IMP may be shipped to the study sites and any patient is exposed to a study-related procedure.

The Sponsor, the Investigator, and any third party (e.g., CRO) involved in obtaining approval must inform each other in writing that all ethical and legal requirements have been met before the first patient is enrolled in the study.

## 10.3 Patient Information and Informed Consent

The Investigator will obtain freely given written consent from each patient after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspect of the study which is relevant to the patient's decision to participate. The informed consent form must be signed, with name and date and time noted by the patient, before the patient is exposed to any study-related procedure, including screening tests for eligibility.
For patients not qualified to give legal consent, written consent must be obtained from the legal parent/guardian. If children are old enough to understand the risks and benefits of the study, they should also be informed and provide their oral or written assent.

The Investigator will explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify. The Investigator will complete the informed consent section of the eCRF for each patient enrolled.

Each patient will be informed that his medical (source) records may be reviewed by the study monitor, a quality assurance auditor, or a health authority inspector, in accordance with applicable regulations, and that these persons are bound by confidentiality obligations.

## 10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the Investigator (Co-ordinating Investigator in multi-center studies) and the Sponsor prior to its implementation. Any such amendments will be submitted to the IEC/IRB and/or competent authority responsible as required by applicable regulations.

IEC/IRB approval will, at a minimum, be requested for any change to this protocol which could affect the safety of the patients, the objective/design of the study, any increase in dosage or duration of exposure to the IMP, an increase in the number of patients treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

## 10.5 Confidentiality of Patient Data

The Investigator will ensure that the patient's confidentiality is preserved. On CRFs or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by a unique patient identifier. Documents not intended for submission to the Sponsor, i.e., the confidential subject identification code list, original consent and assent forms, and source records, will be maintained by the Investigator in strict confidence.

# 11 QUALITY CONTROL AND QUALITY ASSURANCE

## 11.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries compared to source data. The Investigator will co-operate with the monitor to ensure that any discrepancies identified are resolved.

For this study, the first monitoring visit shall take place shortly after the inclusion of the first patient. Thereafter, monitoring frequency will depend on study progress.

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the clinical study. Source data will be available for all data in the eCRFs, including all laboratory results.

## 11.2 Audit and Inspection

The Investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the Sponsor, or to IEC/IRB/regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the patients have been adequately protected, and that all data relevant for the assessment of safety and efficacy of the IMP have been reported to the Sponsor.

# 12 REPORTING AND PUBLICATION

## 12.1 Clinical Study Report

A clinical study report (in accordance with relevant guidelines and the Sponsor's SOPs) will be prepared by the Sponsor after completion of the study. The Co-ordinating Investigator will approve the final study report after review.

## 12.2 Publication Policy

The results of this study may be published or presented at scientific meetings.

If this is envisaged by an Investigator, the Investigator agrees to inform the Sponsor and to submit all manuscripts or abstracts to the Sponsor prior to submission to an editorial board or scientific review committee. This will allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the Investigator.

In accordance with standard editorial and ethical practice, the Sponsor will support publication of multi-center studies only in their entirety and not as individual center data. Authorship will be determined by mutual agreement.

# 13 LIABILITIES AND INSURANCE

In order to cover any potential damage or injury occurring to a patient in association with the IMP or participation in the study, the Sponsor will contract insurance in accordance with local regulations.

The Investigator is responsible for dispensing the IMP according to this protocol and for its secure storage and safe handling throughout the study.

# 14 REFERENCES

Not applicable.

# 15 APPENDICES

Not applicable.